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THE CHICAGO MEDICAL SCHOOL
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MULTIPLE MYELOMA*

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Multiple myeloma is the most neglected of the so-called malignant blood diseases in spite of the fact that it is by no means rare. It is most unusual, for example, not to have a case available for demonstration on the wards of the Cook County Hospital and on one occasion, there were three cases on one ward at the same time.

Why then is multiple myeloma so neglected? There are two special reasons. The first of these is the impossibility of making a definite clinical diagnosis without the aid of laboratory tests and the other is the therapeutic pessimism which resistance to treatment has engendered. This is true in spite of the fact that the condition has been well recognized and adequately described for over a century.

"Mr. M., a highly respectable tradesman, aged 45, placed himself under my care on the 30th of October, 1845. He was then confined to the house by excruciating pains of the chest, back, and loins from which he has been suffering, more or less for upwards of twelve months.

"Mr. M. was now much emaciated; his face was thin and sallow; his aspect expressive of suffering, though, when not actually under the influence of pain, he maintained his natural composure and habitual cheerfulness. The heat of the surface was below the natural standard, the pulse 86, and deficient in strength; the tongue furred; the appetite keen, often voracious, but the thirst not inordinate. The bowels were stated to be generally sluggish, but easily excited to diarrhoea, and the urine was reported to be natural in appearance and quantity.

"For some days previous to our visit, the pain, which had usually occupied the trunk generally, became fixed in the left lumbar and iliac regions, obliging the patient to observe a semi-bent posture, on account of the agony caused by every attempt at movement of the body upon the thighs."

William MacIntyre, who in 1850 thus described a *Case of Mollities and Fragilitas Ossium,* is usually credited with "godfathering" the disease, though in his paper numerous references are made to preceding discussions and descriptions, some even with woodcuts showing the characteristic bone changes of the disease. Regardless of priority, the paper of MacIntyre represents not only a masterful and detailed description of the clinical course of the disease and the autopsy findings, but also for the first time calls attention to the abnormal protein found in the urine, the protein which Henry Bence-Jones studied and which to this time bears his name.

"As some amount of oedema had been observed at one period during the progress of the patient's illness, I procured a portion of his urine for examination. This specimen was opaque, acid, and of

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high density, the specific gravity being 1.035, but it gave no indication of the presence of sugar to Tromer's or to Moore and Palmer's tests. Treated by heat to ebullition, but not under that point, it was found to abound in animal matter, which, when isolated in this way, exhibited all the characters of albumen. With nitric acid, however, this urine displayed anomalies of a remarkable kind. On the addition of the acid no immediate precipitation took place; on the contrary, the urine, previously cloudy or turbid, became instantly clear, and retained its transparency for an hour or an hour and a half, when it was found to have formed into a firm yellow mass, which unlike the coagulum resulting from the action of nitric acid upon serum sanguinis or ordinary albuminous urine, underwent complete solution on the application of heat, but again consolidated on cooling. Such were the effects when operating with the acid at the ordinary temperature of the atmosphere. When, however, the urine was previously heated to ebullition and while still fluid, allowed to cool down a few points, the coagulum was almost instantly obtained, and like that resulting from the slow operation in the cold, suffered redissolution on the temperature being raised to the boiling point."

The name "Multiple Myeloma" was coined by von Rustizky who published a paper under this name in 1873. Kahler, whose name is eponymically linked to the disease in the European literature, in 1889, laid down four diagnostic criteria. These were: bone pain, deformity and pathologic fragility of bone, cachexia, and Bence-Jones proteinuria. For many years these criteria held. Today we define multiple myeloma as a condition characterized by either a focal or a diffuse *abnormal* overgrowth of plasma cells, an overgrowth which in turn may lead to bone lesions with pain and pathologic fractures, elevations in the various globulin fractions of the serum, Bence-Jones proteinuria, kidney damage, and so on, but the keystone of the disease remains the plasma cell overgrowth.

Multiple myeloma is a disease of advanced middle life, 80 per cent of the patients being over 40 and the average age being about 55. The youngest patient we have encountered was 19 and the oldest reported was 92. In most series, males outnumber females 2 or 3 to one, but in our own clinic the ratio is about one to one.

Unless one is constantly on the lookout for the disease, most cases will be diagnosed accidentally. (Table I). Yet there are classical symptoms and signs which should make one suspect the diagnosis (Table II).

TABLE I

Findings Leading to the Diagnosis of Multiple Myeloma

Osteolytic Bone Lesions	36%
Unexplained Anemia	10%
Increased Serum Globulin	10%
Plasma Cells in Blood	8%
Suspected Pernicious Anemia	6%
Bone Pain, Weakness, Anemia	6%
Collapsed Vertebra with Myelitis	4%
Biopsy of Bony Swelling	4%
Bone Tumor	2%
Positive Bence-Jones Proteinuria	2%
Diagnosed Previously	6%
Diagnosed at Post Mortem	4%

TABLE II

Findings in Multiple Myeloma

Increase of Plasma Cells in Marrow	94%
RBC Level below 3.5	90%
Osteolytic Lesions in X-rays	90%
Albuminuria	80%
Reversed A/G Ratio	70%
Bone Pain	66%
Nitrogen Retention	52%
Hypercalcemia	50%
Bone Tenderness	46%
Bence-Jones Proteinuria	20%
Visible Tumors	12%
Plasma Cells in Blood	8%
Solitary Myeloma	4%

Age 19-79 84% 50-70 years
Sex 1 : 1

Since we have classified multiple myeloma as a "blood disease" let us review the changes encountered in the peripheral blood. The red blood cells are usually reduced in number. Three explanations are offered for this: (1) The

crowding out of marrow by the plasma cells; (2) the azotemia resulting from the kidney damage; and (3) the cachexia, negative protein balance, and the "toxic" effect of tumor anabolism and catabolism. There is often much difficulty in counting the red blood cells, partly because of autoagglutination, partly due to cold agglutinins, and partly because of the precipitation of the excess globulin by the mercury of Hayem's solution. This last difficulty can be obviated by the use of Gower's solution or saline. Doing the counts on a warm chamber will help, in part, to obviate the other difficulties.

The white cells are usually normal in number but may be low, and occasionally, as in the so-called plasma cell leukemia, are markedly elevated.

The platelets are for the most part numerically intact, yet clot retraction may be completely absent or very poor.

Yet, it is not these changes in the blood which are the most interesting, but rather those seen in the blood film. Unstained, the preparations may look greasy, and when stained, a pinkish blue background characterizes the films. This background probably represents the staining of the excess protein. Furthermore, the red blood cells, instead of appearing singly, will be seen to be clumped, forming aggregates or rouleaux. This is so characteristic that a good technician will suspect myeloma from these clues. The rouleaux formation and tendency for autoagglutination, phenomena related to the alteration in the globulin and fibrinogen fractions, will alter the rate of red blood cell sedimentation so that the sedimentation rate will be markedly accelerated—furnishing us with still another of the very characteristic features of the disease.

But in the final analysis, it is the marrow which is most important both diagnostically and from the standpoint of initiating the chain of events which "lead but to the grave." It is in the marrow that we find the characteristic plasma cells (Fig. 1), so long a center of controversy. It is only of late that it has been generally accepted that the plasma cell is the common denominator of all multiple

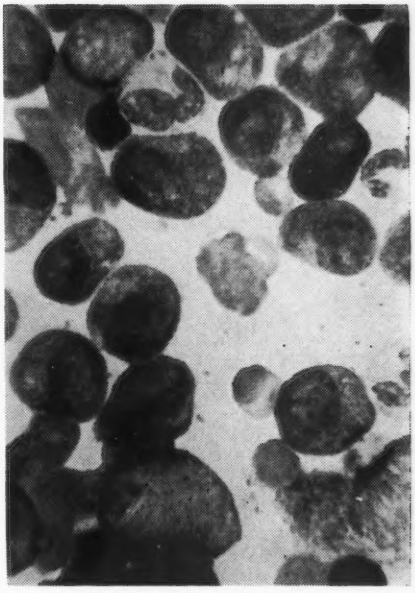


Figure 1
Extensive marow replacement by moderately mature plasma cells.

myelomas. It is not difficult to understand the reason for the old controversies since the cell types in multiple myeloma show considerable variation. However, this variation is within the plasma cell line. If we may borrow the analogy from the leukemias, the relatively benign, *chronic* multiple myelomas have as their characteristic cell the mature "typical" plasma cell (Fig. 2) with the cartwheel nucleus, the Hoff, and the vacuole in the thick blue-gray cytoplasm, whereas the more *acute* multiple myelomas are characterized by primitive cells, not showing characteristic differentiatioin, but rather a tendency of syncytial arrangement and a definite resemblance to primitive reticuloendothelial cells. (Fig. 3).

The recognition of these different cell types is not only important diagnostically but prognostically as well, and it is not unlikely that as more is learned of the proteins elaborated in multiple myeloma, a correlation will be found between the cell types and the specific proteins.

That a hyperproteinemia accompanies the disease was recognized first by Ellin-

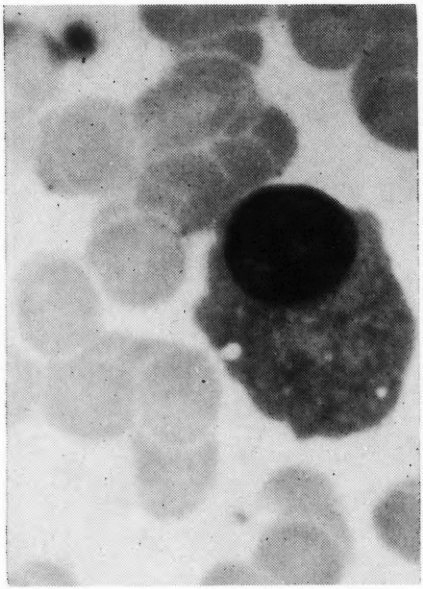


Figure 2
"Typical plasma cell" showing cartwheel arrangement of nuclear chromatin, a peri-nuclear Hoff, and peripheral vacuole. The red cells show clumping and rouleau formation.

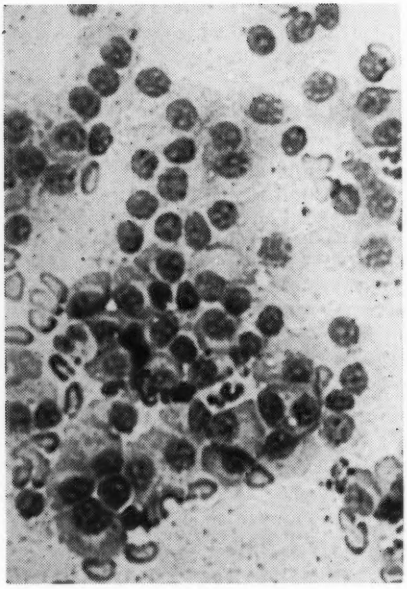


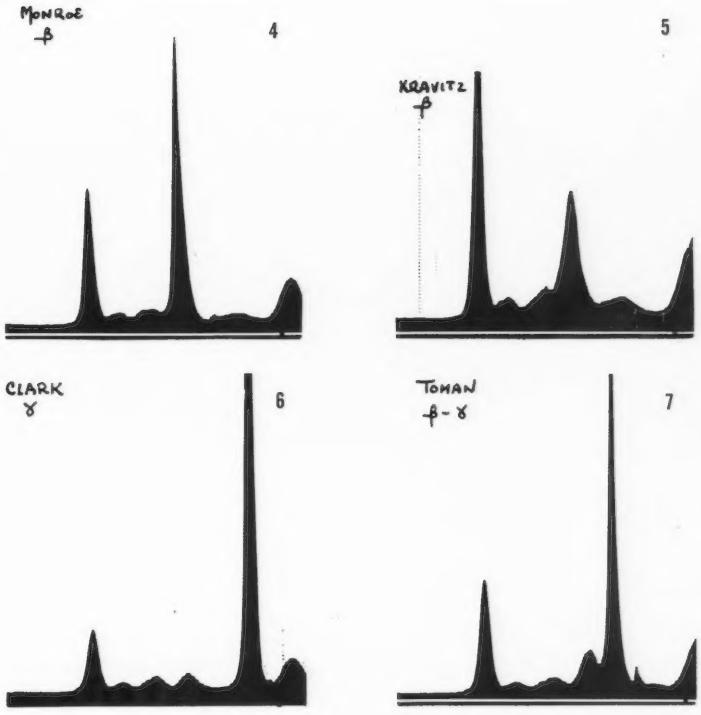
Figure 3
Syncytially aranged immature plasma cells. Several cells show double nuclei.

ger in 1899. In almost all series, this finding has been substantiated in over 50 per cent of the patients. The excess protein is made up of a galaxy of proteins, composed of cryoglobulins, euglobulins, and pseudoglobulins I and II. Electrophoretic studies have given varied results, but patterns with tall narrow peaks in the beta region, in the gamma region, or intermediate between the beta and gamma regions are virtually diagnostic of multiple myeloma (Figs. 4-7). There are, however, cases, otherwise typical, in which these electrophoretic anomalies are absent. The highest protein reported has been 23.27 gm./100 cc., which on fractionation, revealed albumin 1.63, globulin 16.02, and fibrinogen 5.62. More usual is an elevation of protein from 7 to 10 gm., with the globulins representing 5 to 8 gms. of the total.

One of the extraordinary globulins found in multiple myeloma is cryoglobulin. As indicated by its name, it is a cold precipitable globulin. This is probably related to beta or gamma globulin, as judged by its amino acid pattern, though it is thought by some to be a pseudo-globulin. It is soluble in warm water and is thought to play an important role in increasing the viscosity of the blood. When present in large quantities, it is found as a solid white mass between the sedimented red blood cells and the supernatant plasma. Its precipitability is reversible by heat. Cryoglobulins are also found in other conditions such as leukemia, Kala Azar, and arthritis, but large amounts are found exclusively in multiple myeloma.

Apitz has proposed that the plasma cells give rise to a group of closely kindred pathologic proteins which he has termed "paraproteins" and which are characterized by ready precipitation, ready crystallization, and an affinity for Congo red. Some of these abnormal proteins have molecular weights of about 400,000 as contrasted to 70,000 for albumin, 160,000 for gamma globulin, and about 42,000 for Bence-Jones protein.

Of all the interesting findings in multi-



Figures 4 to 7

Various electrophorectic patterns in multiple myeloma.

ple myeloma, the outstanding is Bence-Jones proteinuria. This is true in spite of the fact that it occurs in only from 50 to 60 per cent of the cases, and that it may also be found in leukemia, metastatic carcinoma of bone, osteomalacia, multiple fractures, and fibrocystic bone disease. Bence-Jones protein is also present in normal marrow, where it is thought to represent an extract of plasma cells. In general, Bence-Jones protein in the urine bears an inverse relation to the protein content of the blood. Its fundamental abnormality lies in its being precipitated by heat in the range of about 45 to 60° C. and its ready solubility below and above this range.

"The most striking peculiarity which distinguished this from any other specimen of urine I ever examined, and in an especial manner from that excreted in Bright's disease, was its behaviour with nitric acid. The reaction of nitric acid and ordinary albuminous urine are so uniform and constant, that they are received as the most trustworthy evidence of the presence of albumen, the acid never failing to produce an immediate and notable coagulation in urine containing the foreign ingredient. But in our patient this familiar and convenient test failed, like heat, to give any immediate intimation of the presence of animal matter. On the contrary, the absence of albumen was, in the first trials, not unnaturally inferred from the circumstance of the urine, previously hazy, becoming instantly clear on dropping the nitric acid into it; and it was only on inspecting the test tube some hours afterwards, that its contents were seen to have undergone the remarkable change already described. I was at first inclined to think that some mistake had occurred,

but on repeated trials with other specimens, and closely watching their course, the results were always found to be the same."

There has been little added to our knowledge of the behaviour of Bence-Jones protein since it was studied by MacIntyre and Bence-Jones over a hundred years ago.

"But enormous as was the quantity of animal matter thus shown to have been incorporated with the urine, its presence had nearly escaped observation. It is true that its discovery was effected by means of heat and nitric acid, the tests commonly employed, singly or conjointly, for displaying albumen when it exists either as a natural constituent of animal fluids, or as a morbid component of urine; but in the present instance these agents, when employed in the usual way, failed entirely as tests, and it was not until they were applied in a modified manner, that they succeeded in detecting and disengaging the alien ingredient, displaying at the same time a set of novel and remarkable reactions which seemed to bespeak the existence of some special disease bearing but a distant relation to any of those derangements of function or structure which we are accustomed to associate, in a pathological sense, with ordinary albuminuria."

Because of the precipitation of Bence-Jones protein in the renal tubes and the formation of casts which block the nephrons, an intrarenal hydronephrosis is produced. As a consequence, albumin, casts, renal epithelial cells, low concentrating power, and low dye excretion are concomitant effects of the disease. An ingenious way of producing a simulated Bence-Jones protein using the white of an egg was described by Owren in 1950.

Other significant blood changes worthy of mention are the frequent increase in calcium and phosphorus due to their liberation from bone, the retention of nitrogen without elevation of the blood pressure and without red blood cells or white blood cells in the urine due to the above mentioned hydronephrosis, and the elevation of uric acid due to the increased nucleoprotein metabolism. The hypercalcemia and hyperphosphoremia may lead to difficulty in the differentation between multiple myeloma and hyperparathyroidism.

Still another interesting relationship is that of multiple myeloma to amyloidosis. This was first described by Adams and Dowse in 1872 and is to be distinguished from secondary amyloidosis in that the former does not usually occur in parenchymatous organs, but rather in the walls of blood vessels and in the heart, trachea, lungs, and tongue, though it has also been reported in many other locations. This, however, is not a certain differential diagnostic criterion since it may be found in the spleen, liver, kidney, and adrenals. Occasionally, when it occurs in muscles, joints, and periarticular tissues, differential diagnosis from rheumatoid arthritis is very difficult. The amyloid itself is usually within the myeloma and appears to be a homogeneous amorphous material which stains pink with hematoxylin and eosin, metachromatically with methyl violet and methyl green, yellow to pink with Van Gieson connective tissue stain, and pink to red with Congo red. The amyloid may also be found in the myeloma cells, or in small masses surrounded by giant cells. Chemical studies show no constant composition, the amyloid varying in make-up in different sites.

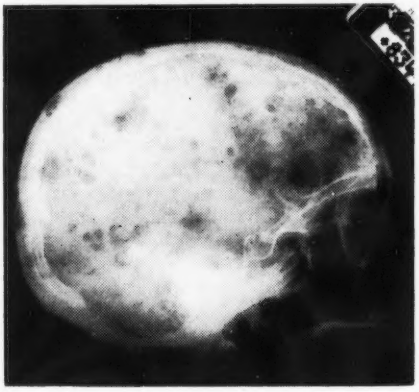


Figure 8

X-ray of skull showing typical punched-out lesions without bone formation around the area of rarefaction.

Pathologic features of the disease have been alluded to throughout the foregoing discussion. The distribution of the plasma cells may be such to form a singular tumor — a solitary myeloma — which occasionally, following surgical removal and x-ray therapy, is curable. More commonly the tumors are multiple and give rise to the typical punched out bone lesions surrounding which no new bone formation is seen in the x-ray (Fig. 8). Sometimes these lesions become large and the cortex of the bone is remarkably displaced (Fig. 9). Any bone containing red marrow may show involvement. MacIntyre's description is masterful.

"On dividing the cartilages at the usual place, it was found that the adjoining extremities of the osseous ribs crumbled under the heel of the scalpel, and on prosecuting the dissection it was discovered that all the ribs, throughout their whole length, were soft and brittle, so that they could be easily cut by the knife, and readily broken, at any point by the exertion of a very moderate force. They had evidently lost much in size and weight, as well as in consistency and tenacity; their outer casement, or laminated portion, was very thin, loose and fragile, yielding and crackling when pressed between the fingers and thumb; their interior was charged with a soft gelatiniform substance of a blood-red colour and unctuous feel. The sternum was in a similar state of softening and fragility, . . ."

Occasionally there are no tumors, but rather a diffuse involvement of the osseous system, giving the appearance of a diffuse osteoporosis on x-ray and that of an aplastic anemia on blood examination. In still another variant, extraosseous tumors are prominent. These may occur in a number of sites, of which the testes, ovaries, tonsils, lung, heart, pancreas, adrenal, intestine, and gallbladder are examples. With any of these forms, plasma cells in numbers may appear in the peripheral blood giving rise to plasma cell leukemia.

The changes in the kidney are pathognomonic when typical. Crystalloid hyalin-like casts plug the renal tubules, particularly in the lower portions of the nephrons. Polymorphs and giant cells often surround these. The tubules frequently become dilated, and interstitial scarring may occur, but the glomeruli and vessels remain intact. The tubular epithelium may show granular, vacuolar, and hyaline degenerative changes with a tendency toward desquamation. Calcification may be prominent, especially in the kidney, due to the hypercalcemia, but this may also be seen elsewhere. Occasionally, pyelonephritis complicates the kidney picture because of spinal cord injury.

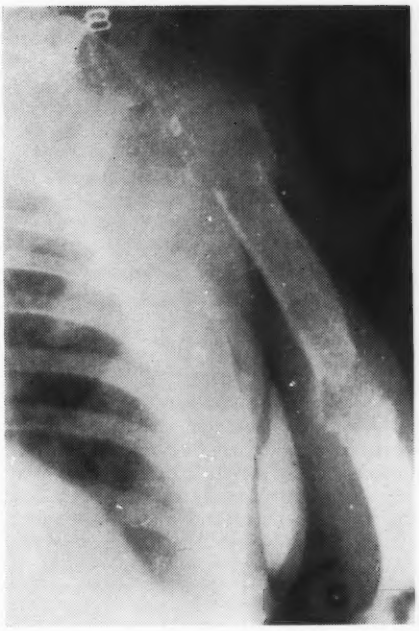


Figure 9

Extensive involvement of humerus by myeloma with almost total destruction of cortical bone.

Due to the greatly increased blood viscosity spontaneous intravascular clotting may occur leading to thrombotic accidents and infarcts.

Because the nucleoproteins of myeloma cells are probably different from those of other cells, it was thought possible by Snapper that the protein is more readily displaced by stilbamidine. For this reason stilbamidine was given a therapeutic trial some years ago and, even though stilbamidine was demon-

strated in the myeloma cells, the drug did not prove to be therapeutically useful. X-ray, P_{32}, antimony, ACTH, Cortisone, and other agents have also been tried and found wanting. During the last two to three years there has been some enthusiasm for ethyl carbamate (Urethane). Occasional recalcification of bone and even reappearance of trabecular pattern have been reported. Most important of all, there has been alleviation of pain, a very distressing feature of the disease.

". . . the patient, now almost constantly racked with pain, was unable to leave his bed; he lost his appetite, took scarcely any nourishment, and on the first of January died exhausted, in the full possession of his mental faculties, and evincing, in his supreme hour of suffering, the same admirable fortitude and patient endurance which he had displayed throughout the whole course of his trying illness."

Ultimately, however, all the patients, like Mr. M., die, with an average life expectancy of about 2 years from the time the diagnosis is made. This interval will increase as the diagnosis is made earlier by the more widespread use of marrow examination. An occasional patient will live for quite some time, ten years having been reported as the maximum life expectancy.

This then is the story of the little progress in the hundred-odd year history of this disease. For the moment the plea must still be for correct diagnosis: "On this point the remark of Mr. Curling is not to be disregarded, *viz,* that we should bear this disease in mind when treating pains of the limbs of an obscure and intractable character." This will be facilitated by our being ever mindful of the condition and having better diagnostic tools. MacIntyre closes his paper as follows: ". . . the ordinary means of examination at the command of the practical physician unversed in the nice processes of analytical chemistry, were sufficient to bring me acquainted with physical properties and chemical reaction, which, independently of their apparent direct relation to the disease which destroyed the patient, seemed to me deserving of a detailed account; and I shall be content if I have succeeded in pointing out to future observers, gifted with the requisite qualifications for conducting researches of a higher order, certain definite and distinctive characters by which a particular and hitherto unrecorded pathological condition of the urine may be recognized and identified."

It is to be hoped that we shall *not be content* simply to have pointed out interesting phenomena but shall strive to find the cause and cure of this strange disease, and so complete its history.

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THE MYTH OF THE INTERCELLULAR CEMENT AND CAPILLARY PERMEABILITY

HANS ELIAS, Ph.D.*

A hypothesis is the result of observations and subsequent speculation. Since speculation is admitted to be subjective, it is customary to test a hypothesis by experimentation or by critical observations. If the hypothesis passes these tests, it may acquire the status of a theory. However, if the material is of such a nature that testing is impossible, the hypothesis cannot be tested and its validity is therefore questionable.

Chambers and Zweifach[1] stated that, in their opinion, most substances which pass through the walls of blood capillaries pass through a hypothetical intercellular cement rather than through the endothelial cells. This hypothesis, presented by Chambers and Zweifach merely as an opinion, has acquired, in the minds of others, the rank of a theory and it is being used by some as if it were a fact. It has even found its way into certain textbooks, *e.g.,* Ham[2]. Certain authors have ascribed capillary fragility to a destruction of this hypothetical intercellular substance[3]. This metamorphosis of an opinion into supposed established truth is the result of the failure of those who have accepted it to read *carefully* the original paper by Chambers and Zweifach. Subsequent authors copied from one another, accepting blindly the temporary opinion of two distinguished scientists, who themselves did not intend to do more than to make a suggestion. This pseudo-theory has become well established by frequent repetition, and a fairly large body of literature has been accumulated which is based on it.

The originators of the hypothesis made careful studies on the permeability of the capillary wall and found that substances of small molecular size move through it in perfect obedience to the laws of osmosis. Chambers and Zweifach seem to have been greatly disturbed by this observation, which indicated that the capillary endothelium behaved, in regard to osmosis, exactly like an inanimate membrane. Living cells, they felt, should behave mysteriously. They state, "If the passage of materials (through a cell) is a sole property of colloidal and hydrostatic pressure differences, then our whole concept concerning cell life falls to the ground."

This statement is the only evidence presented in favor of the intercellular cement hypothesis. Obviously, it is a statement of a conviction, the conviction that living cells are different from inanimate matter as far as permeability is concerned. While this is true for specific cells(as for example those lining the proximal convoluted tubules), it is not necessarily true for *all* cells. No evidence has been presented that endothelial cells should not possess a physically understandable permeability.

Chambers and Zweifach, after claiming that the intercellular cement plays a predominant role in cell permeability, postulated a specific structure of the cement lines. In their opinion, these lines possess pores of such size that they allow the passage of full plasma. Under normal conditions, however, they assume that a layer of serum protein is adsorbed to the supposed cement substance, decreasing the size of the pores and thereby preventing large molecules from passing through.

Sokoloff[4] claims to have demonstrated the pores microscopically by treatment with tannin ferric chloride. Sokoloff "documents" his statement by means of a drawing (not a photograph) which shows intercellular cement lines approximately 3 μ wide, perforated by pores approximately 1.5 μ in diameter. These measurements are estimated by the present writer, based on comparison with the size of an endothelial nucleus which is

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also shown in the same drawing. The endothelial nuclei are known to be 10-20 μ long. If Sokoloff's drawing were correct, not only the largest molecules, but even entire micro-organisms could pass through the pores. No other claims have been made in the literature for the optical demonstrability of these pores.

As every histologist knows, the boundaries of endothelial (as well as of mesothelial) cells can be determined by silver impregnation. These lines are so fine that they are distinguishable only with difficulty at high magnification. They are certainly not wider than 0.4 μ, being very close to the resolving limit of the light microscope. The average endothelial cell, when distended, is approximately 30 μ long and 10 μ wide. In other words, its average diameter is 20 μ. Consequently, the total surface of the intercellular cement is less than 1/50 of the total surface of the capillary—and even this is an overestimation. We must assume that the visible line consists of a deposit of metallic silver in the neighborhood of the actual line of adhesion. The adhesion line must therefore be much narrower. Since it is invisible during life and since it cannot be visibly stained (a silver deposit is not a stain), it may be assumed that the actual boundary line is below the limit of microscopic visibility. In other words, it is probably narrower than 0.2 μ. This brings the total surface of the cement down to less than 1/100 of the wall surface. Since the only known function of a capillary is the passage of substances through its wall, it appears extremely improbable that most of these substances should pass through such a small fraction of the total surface area.

Warren H. Lewis[5] has demonstrated that living mesenchymal cells are mutually adhesive by the sticky character of their cell membrane. It is also known that discrete bodies of rubber, if uncoated, are strongly adhesive. We make practical use of this property when repairing inner tubes. Even coagulated protein will adhere firmly to glass, as evidenced by the fact that histological sections stick to the slide without the use of albumin — if the slide is perfectly clean. Therefore, there is no *a priori* reason to believe that a special cement substance holds the endothelial cells together. It seems more probable to assume that the endothelial cells are so sticky that they adhere to each other without the interposition of any cement. Their internal coating of serum protein prevents the opposing capillary walls from sticking together. From the mechanical aspect, the serum protein coat is comparable with the coat of powdered sulfur used to prevent the opposite walls of an inner tube from adhering to one another.

To explain the silver nitrate lines, the following hypothetical arrangement is suggested:

At the place where two endothelial cells meet, the opposing surfaces are rounded off while the internal protein coat is a continuous, flat membrane. Thus, an interstitial space of prismatic cross section is formed. Frederic T. Lewis[6] has demonstrated that wherever three cells or three bubbles meet, such a triangular, prismatic interstitial space exists. F. T. Lewis gave this space the name "edge canal." Its existence and size depend on the mutual relationship of surface tension and adhesiveness. It is suggested that the silver is deposited within this edge canal which is bounded by two endothelial cells and the inner coating of the capillary.

In all probability, therefore, no intercellular cement exists in the endothelial wall of capillaries. Since it probably does not exist, it cannot play any role in the transmission of substances. It is claimed, as has been reported above, that destruction of the intercellular cement is responsible for capillary fragility. In the light of the probable non-existence of that cement, this hypothesis cannot be maintained.

There are two other possibilities which may account for the phenomenon of capillary fragility and increased permeabil-

ity: (1) the exoplasm of the endothelial cells may lose its adhesive quality; (2) the pericapillary basement membrane may be weakened in spots. Photomicrographs by Wexler and Branower[7] seem to strongly support the latter viewpoint. These authors showed microaneurysms of the retinal vessels in diabetic and hypertensive patients. The microaneurysms are local spherical enlargements of the capillaries, but the capillary wall as a whole is not interrupted. It appears rather that the pericapillary basement membrane is locally softened so that the intracapillary pressure is able to produce the aneurysm. Under these circumstances, the endothelial cells must become greatly distended, thereby altering their osmotic properties. They may become mutually detached or ruptured. Destruction of intercellular cement, if it existed, could not produce microaneurysms, but would rather result in a breaking, without thickening, of the capillaries.

It is further claimed that ascorbic acid and rutin prevent capillary fragility by maintaining the intercellular cement. While the beneficial action of these substances cannot be denied, it is, however, suggested that they aid in the maintenance of the pericapillary basement membrane and of the accompanying reticular and elastic fibers.

Summary

The opinion pronounced by Chambers and Zweifach that a hypothetical intercellular cement plays an important role in the permeability of endothelial walls is shown to be untenable. The opinion was based on vitalistic convictions and was not supported by observed evidence. The very existence of an intercellular cement in endothelium is doubtful. The classical theory assuming that the exchange of substances occurs through the living endothelial cells is re-established.

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EXPERIMENTAL HYPERTENSIONS*

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The reproduction of a given human disease in experimental animals has frequently led to a solution of its pathogenesis and to more effective treatment. Accordingly, many attempts have been made to produce essential hypertension experimentally. This clinical condition accounts for 95 per cent of all patients with hypertension seen by physicians. Essential hypertension is relatively common since approximately 15,000,000 people in the United States are estimated to have hypertension and morbidity and mortality from hypertension are exceeded only by morbidity and mortality from arteriosclerosis in the Western World. "Hypertension" expresses the cardinal sign of the disease; "essential", our comparative ignorance of its cause.

The known causes of hypertension, accounting for only approximately five per cent of patients with this sign of disease, are best classified into renal, cerebral or neurogenic, endocrine, and cardiovascular. It is highly important to differentiate these hypertensions of known causes from hypertension of unknown cause or essential hypertension. This is so because in some of the former patients a complete cure of the hypertension is possible, whereas therapy of essential hypertension is less satisfactory. Thus when a unilateral renal anomaly, renal tumor, or unilateral pyelonephritis is responsible for the hypertension, nephrectomy may be curative. Likewise, surgical removal of adrenocortical tumors and of pheochromocytomas has resulted in cure of the hypertension. Cure of hypertension may also follow operative removal of a segment of constricted aorta.

Methods of Producing Experimental Hypertensions

The production of experimental hypertension has involved three main avenues of approach; *viz.*, the nervous system, the endocrine glands, and the kidney, each of which has been considered as involved in the pathogenesis of essential hypertension.

(a) Nervous System. Experimental hypertension following changes produced in the nervous system has been reported from (1) the injection of a kaolin or aluminum silicate suspension into the cisterna magna; (2) the production of intracranial ischemia by the ligation of arteries supplying the brain; (3) the application of repeated and strong auditory stimulation; and (4) the section of the aortic depressor and carotid sinus nerves (so-called buffer nerves).

(1) Some years ago a number of laboratories in Europe and in this country reported that the injection of a kaolin suspension into the cisterna magna produced hypertension in dogs and other animals presumably by setting up a chemical meningitis with resulting increased intracranial pressure. However, our research group and others have recently proved conclusively that no hypertension is produced by this means. The older results were obtained with the cuff method of measuring blood pressure which is notoriously inaccurate when applied to the thigh of the dog because of frequently occurring increased skeletal muscle tonus in the conscious animal. Recent negative results were obtained with the accurate direct method of needle puncture of the femoral artery.

(2) Some dogs subjected to successive ligation of the carotid and vertebral arteries and subsequently to ligation of some of the developing collateral vessels show a degree of cerebral ischemia and hypertension, which, however, has not proved sufficiently consistent or pronounced for extensive study.

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(3) Rats selected for their emotional instability develop hypertension when subjected to repeated strong auditory stimulation with a blast whistle. Obviously this form of hypertension involves changes in the nervous system, the nature of which have not yet been determined.

(4) Section of the buffer nerves of dogs leads to hypertension due to the loss of the normal inhibitory effect of these nerves on the vasomotor or vasoconstrictor center and mechanism, thereby producing increased tonus of the arterioles and increased peripheral resistance. This form of hypertension, however, differs in several important respects from essential hypertension; *viz.*, there is an increased cardiac output in this experimental hypertension whereas the cardiac output is normal in essential hypertension; the heart rate is increased in buffer nerve hypertension but is normal in essential hypertension; and the buffer nerves no longer function in this form of experimental hypertension whereas they do function in essential hypertension, though at higher blood pressure levels. However, there are certain similarities between this form of experimental hypertension and essential hypertension. Thus, buffer hypertension involves increased tonus of systemic arterioles and certain sympatholytic drugs such as dibenamine, dihydroergocornine, and SKF 688-A, reduce the blood pressure of these hypertensive dogs and also the blood pressures of some hypertensive humans. Moreover, many patients with essential hypertension show evidence of cortico-hypothalamic imbalance which may in turn cause increased activity of the posterior hypothalamus, the vasoconstrictor center, and the vasoconstrictor nerves. Hence, this form of experimental hypertension should be subjected to more study by investigators in the field of hypertension than at present.

(b) Endocrines. From the endocrine standpoint, experimental hypertension has been reported as induced by (1) the continuous intravenous infusion of epinephrine or adrenaline, (2) reduction in the blood supply to the adrenal gland by ligation of some of the blood vessels of the gland, (3) the administration of desoxycorticosterone, and (4) the injection of certain anterior pituitary extracts.

(1) Dogs subjected to continuous intravenous infusion of epinephrine maintain an elevated blood pressure during the period of their survival which is usually about two weeks. At the end of this time, the animals die from causes which are poorly understood, although gastrointestinal disturbances are involved. Obviously this form of experimental hypertension is not suited for long-term study and, more important, there is no increase in the epinephrine concentration of the blood in essential hypertension. On the other hand, this experimental hypertension is similar to that produced in patients by tumor of the adrenal medulla (pheochromocytoma). Actually these tumors are now known to produce a mixture of epinephrine and nor-epinephrine, usually with the latter in larger amount. Hence, a new experiment might well be tried employing an intravenous infusion of nor-epinephrine or the intramuscular injection of nor-epinephrine in a slow absorption medium. If such an experiment should result not only in hypertension but in prolonged survival, obviously the hypertension of pheochromocytoma and not that of essential hypertension would be simulated.

(2) Reduction in the blood supply to the adrenal gland has been reported to produce hypertension in dogs. All attempts to repeat these findings by several research groups including our own, have met with failure and presently this can not be considered to be a method for the production of experimental hypertension.

(3) Large doses of desoxycorticosterone administered parenterally to rats, particularly with sodium chloride orally, produce hypertension. This is likewise true for the human, including even patients with Addison's disease. However, the method is not particularly successful in the dog. The mechanism of this experimental hypertension is not understood at the present time, although several differences and similarities between it and essential hypertension have been found. Increased tissue fluid and blood

volume resulting from the retention of sodium chloride in the body are probably not the principal cause of this experimental hypertension, although a high salt diet alone in rats, but not in dogs, will produce some degree of hypertension. Although it has generally been assumed that salt hypertension is associated with altered adrenal cortical function and perhaps renal function, recent work suggests that this hypertension is not mediated through either the adrenal cortex or the kidney. In general, it is easier to produce hypertension in the rat than in the dog. Some patients with essential hypertension show alterations in sodium chloride metabolism.

(4) There is ample evidence that a few injections of certain crude and semi-purified anterior pituitary extracts, including growth hormone preparations, will produce hypertension in rats. Findings in the dog have been less consistent. The mechanism of this experimental hypertension has not yet been determined, although there is some evidence that stimulation of increased secretion of one or more adrenal cortical hormones may be involved. Perhaps the adrenal cortex may differentially produce an augmented secretion of an as yet unknown cortical steroid with predominant arterial constricting and blood pressure raising effects and minimal effects on carbohydrate and salt metabolism. In any event, in the present state of our knowledge, this form of experimental hypertension and that due to desoxycorticosterone bear more similarity to the hypertension seen clinically in pituitary basophilism and in adrenal cortical tumors, than they do to essential hypertension.

(c) Kidney. The following methods of modifying renal function have been reported to give rise to experimental hypertension: (1) administration of nephrotoxic substances, (2) x-ray radiation of the kidney, (3) the production of antiserum nephritis, (4) the production of renal damage by a brief period of choline deficiency, (5) partial obstruction of the ureters, (6) partial obstruction of the renal veins, (7) surgical removal of kidney tissue, (8) partial occlusion of the aorta above the origin of the renal arteries, (9) compression of the kidney by a figure-of-eight tie or by a silk, latex, or plastic bag, and (10) constriction or partial occlusion of the renal arteries.

(1) Various substances toxic to the kidney, such as uranium nitrate, mercuric chloride, diphtheria toxin, and streptococcal cultures have been reported inconstantly to produce a low grade hypertension in a minority of animals given these agents.

(2) X-ray radiation of the kidney area in dogs and other animals has produced a low-grade hypertension in an occasional animal.

(3) Experimental antiserum nephritis in rats and dogs has been found to produce hypertension in some of the rats and in an occasional dog. However, this hypertension would appear to resemble that seen in human glomerulonephritis rather than essential hypertension.

(4) A brief period of deficiency in the lipotropic substances, choline and methionine, in weanling rats, followed by a normal diet for three to five months results in hypertension in the animals which survive the acute renal damage induced by the deficiency. A similar regimen for mature rats does not lead to hypertension, nor does prolonged choline deficiency in young or mature rats lead to hypertension. This experimental hypertension is obviously deserving of further study, particularly in other species of animals. Its present classification as a type of experimental renal hypertension is based on the findings that a period of bilateral renal cortex necrosis is a necessary predecessor to the later development of hypertension and that renal decapsulation abolishes the hypertension. On the other hand, this hypertension may be classified as endocrine since the weanling rats also show adrenal cortical enlargement and the administration of adrenocorticotropin restores the hypertension abolished by renal decapsulation.

(5) Partial obstruction of the ureters in dogs produces an inconstant low-grade hypertension which resembles that sometimes seen clinically in partial obstruction of the lower urinary tract rather than essential hypertension.

(6) Partial obstruction of the renal veins gives rise to a low-grade hyperten-

sion in rabbits which may be similar to the hypertension which occasionally is found to develop in patients with cardiac failure and increased venous pressure.

(7) Subtotal nephrectomy in the rat, but not the dog, leads to hypertension. Recent work indicates that this hypertension results from compression of the remaining kidney substance by scar tissue, so that probably this hypertension is similar to that produced by compression of the kidney by means of a figure-of-eight tie or silk bag. Bilateral nephrectomy in the dog with survival for several months by repeated peritoneal lavage has been found to produce hypertension resembling essential hypertension in several respects. However, it appears to differ in one important respect, *viz.*, that an increased interstitial fluid volume is necessary for the hypertension. This hypertension suggests that the kidney may secrete a blood-pressure regulating or depressor hormone, the loss of which results in hypertension. Such a possibility in no way precludes the probability that kidney tissue under certain circumstances can also produce hypertension by giving rise to a pressor hormone or hormones.

(8) Constriction or partial occlusion of the aorta above but not below the origin of the renal arteries leads to hypertension in dogs, demonstrating that the hypertension seen in coarctation, particularly of the lower thoracic aorta in man, is probably partially on a renal basis.

(9 and 10) Compression of the kidney by a figure-of-eight tie, encapsulation of the kidney in a silk bag, and constriction of the renal artery has each been productive of a high level, persistent hypertension in rats, rabbits, goats, sheep, dogs, and monkeys. These procedures may be carried out bilaterally or unilaterally with contralateral nephrectomy. Of these last three techniques for producing experimental renal hypertension, partial constriction of the renal arteries (the classic method of Goldblatt) has proved most satisfactory in our hands.

Relation of Experimental Renal Hypertension to Essential Hypertension

Many studies have been conducted to determine whether experimental renal hypertension produced by constriction of the renal arteries is similar to essential hypertension. Similarity obviously does not necessarily mean even a partial common pathogenesis of the two conditions but similarities encourage research workers to conduct a thorough study of the pathogenesis and treatment of the experimental disease in the hope that our knowledge of the pathogenesis and treatment of essential hypertension may be advanced. Following are the most important similarities between experimental renal hypertension and essential hypertension which have been found so far: (1) The cardiac output, the blood volume, the elasticity of the arteries in early hypertension, and the viscosity of the blood are normal in both conditions. (2) There is increased peripheral resistance in the region of the arterioles, due early to vasoconstriction and later partially to arteriolosclerosis. (3) There is left ventricular hypertrophy. (4) There is arteriolosclerosis conditioned by the duration and severity of the hypertension. (5) The pulmonary blood pressures are normal. (6) The erythrocyte and leucocyte counts are essentially normal in early hypertension. (7) There are no significant changes in endocrine functions with the exceptions of the anterior pituitary and the adrenal cortex, both of which show some evidence of altered function. (8) The more common, less sensitive tests for renal function give essentially normal results. (9) Blood chemistry findings are normal. (10) There is reduced renal blood flow in most renal hypertensive dogs and in most patients with essential hypertension, although some patients and some dogs show normal renal blood flow. (11) Increased amounts of renin appear in the blood following acute constriction of the renal artery of dogs and humans, although there is no significant difference in the renin concentration of the plasma of chronic renal hypertensive dogs or essential hypertensive humans as compared with normotensive dogs or humans. However, recent work demonstrated that a sustained blood pressure increase can be maintained in rabbits by an amount of semipurified rabbit renin administered by intravenous drip which

would raise the plasma renin concentration so slightly as to be beyond the most sensitive assay method for renin presently available. (12) Increased amounts of another renally produced vasoactive factor known as VEM (vaso-excitor material) and of a liver-produced vasoactive factor known as VDM (vaso-depressor material), have been found in the blood of chronic renal hypertensive dogs and of humans with essential hypertension.

Furthermore, excessive constriction of the renal arteries of the dog produces a severe and rapidly fatal form of hypertension which is called experimental malignant hypertension. This closely resembles what is probably a very severe, rapidly fatal variety of essential hypertension, *viz.*, malignant hypertension.

While comparisons have shown these and other similarities between experimental renal hypertension and essential hypertension, only three apparent differences between the two conditions have been suggested thus far: (1) Complete sympathectomy in dogs neither prevents the production of experimental renal hypertension nor influences it significantly when already established. On the other hand, about 10 per cent of patients with essential hypertension obtain what appears to be tantamount to a cure from partial or complete sympathectomy. However, the remaining 90 per cent appear to respond to sympathectomy similarly to renal hypertensive dogs, so far as blood pressure level is concerned. The former group of patients may possibly have their hypertension on a predominantly neurogenic basis. Their hypertension may be different in pathogenesis from the majority group whose blood pressure level is not significantly influenced by sympathectomy, even though some of these patients are undoubtedly otherwise favorably influenced by the procedure.

(2) A suggested qualitative difference between dogs with experimental renal hypertension and humans with essential hypertension is their response to the cold pressor test. This procedure has been stated to produce a greater rise in blood pressure in patients with essential hypertension than it does in humans with normal blood pressure. However, other investigators question whether a significant difference exists. In renal hypertensive dogs, the increase in blood pressure is no greater than in dogs with normotension.

(3) While some patients with essential hypertension die of other disease processes or of old age, a majority of those seen by physicians ultimately succumb to heart failure, cerebral hemorrhage, or, less frequently, to renal failure. On the other hand, renal hypertensive dogs die of old age, intercurrent infection, cancer, or, rarely, renal failure but never from heart failure or cerebral accident. Likewise, renal hypertensive dogs show much less arteriosclerosis than patients with essential hypertension. This, however, is not evidence for dissimilarity between experimental renal hypertension and essential hypertension but is more probably evidence for the fact that the cardiovascular system of the dog is more resistant to adverse influences than that of the average human.

Pathogenesis of Experimental Renal Hypertension

The many similarities between experimental renal hypertension and essential hypertension suggest the possibility of at least a partial common pathogenesis for the two conditions and accordingly research workers have been encouraged to study the pathogenesis and treatment of experimental renal hypertension not only to improve our knowledge of renal and cardiovascular functions but also to improve our understanding of essential hypertension. The basic change responsible for experimental renal hypertension following constriction of the renal arteries, usually by means of small silver clamps, is a generalized constriction of the systemic arterioles as a result of increased tonus of the smooth muscle contained in their walls. This constriction of the arterioles could be due either to increased vasomotor control or to the action of one or more substances transmitted by the blood and originating from changes in renal metabolism produced by constriction of the renal arteries. A number of experiments have excluded increased vasomotor control of the arterioles as a factor in experimental renal hypertension. Since a neurogenic basis

for experimental renal hypertension is highly unlikely, much attention has been given to the elucidation of a humoral mechanism originating in the kidney.

For several years there have been three hypotheses seeking to explain the pathogenesis of experimental renal hypertension on a humoral basis; *viz.*, (1) increased elaboration and secretion of pressor amines by the kidney; (2) decreased secretion of a renal blood pressure regulating or depressor substance or hormone; and (3) increased secretion of the renal pressor substance renin and/or other chemically and biologically related substances, such as SPS (sustained pressor substance) and VEM.

(1) The pressor amine hypothesis is based on the concept that a reduced blood flow and, with this, some reduction in the oxygen supply to the kidney, is necessary for the production of experimental renal hypertension. It is by no means certain that these conditions are necessary for the production of experimental renal hypertension, although obviously there is some alteration in renal hemodynamics resulting from constriction of the renal arteries by the clamps. Reduced oxygen supply to kidney tissue in the test tube has been shown to change the activity of certain tissue enzymes in such a way as to cause the formation of increased amounts of amines, such as hydroxytyramine, with pressor effects. Whether or not this occurs in the kidney in experimental renal hypertension still remains to be proved.

(2) The hypothesis that there is a decreased secretion of a blood pressure regulatory hormone by the kidney resulting in hypertension, has better, but not conclusive, evidence to support it. The best evidence produced to date for this hypothesis is the finding of hypertension in dogs following complete removal of kidney tissue, in whom life is maintained for two months or more by means of peritoneal lavage. The hypertension so produced resembles experimental renal hypertension produced by constriction of the renal arteries in some respects but differs in regard to increased interstitial fluid volume.

(3) Renin is a proteolytic enzyme extractable from the cortex of the kidney which acts on a globulin of the plasma (hypertensinogen or renin-substrate) to produce a polypeptide known as hypertensin or angiotonin, which is the actual pressor agent. As previously indicated, no one has yet demonstrated increased amounts of renin in the blood in chronic or late experimental renal hypertension or in essential hypertension. We now know that this failure may be due to the fact that the renin assay methods presently available are not sufficiently sensitive. So far, the strongest evidence for the renin hypothesis in our judgment is the prevention and successful treatment of experimental renal hypertension in dogs with semi-purified hog renin. Since this is a foreign protein, it produces an anti-substance or antibody known as antirenin which not only neutralizes the pressor effect of hog renin but also of dog renin, thus strongly suggesting that the antihypertensive effects are due to the neutralization of the hypertensive dog's renin. However, semipurified hog renin still contains other vasoactive proteins, including SPS. The antihypertensive effect might be due to antibodies to SPS or to other proteins not yet identified in semipurified hog renin.

Treatment of Experimental Renal Hypertension

Although the problem of the pathogenesis of experimental renal hypertension is still only partially solved, work aimed at successful therapy has proceeded apace. Treatment of the experimental condition has followed 8 main avenues: (1) removal of the arterial constriction; (2) nephrectomy or removal of a single kidney when the experimental hypertension has been maintained by unilateral renal artery constriction in the rat or, exceptionally, in the dog; (3) sympathetic blocking drugs; (4) low salt diet; (5) marine oils; (6) the pressor amine, paredrine; (7) repeated courses of crude anterior pituitary extract; and (8) renal extracts.

(1) Obviously, removal of the constricting Goldblatt clamp from the renal artery should lead to normotension. The experiment has been performed in rabbits and in dogs which have been hypertensive for six months or more with a resulting return of the blood pressure to

normal. This method of treatment, however, has no clinical application except in rare instances where hypertension has resulted from partial occlusion of the renal artery by pressure from a tumor or from some other neighboring structure. Such a clinical hypertension, of course, would be classified as a hypertension of known cause and not as one of unknown cause or essential hypertension.

(2) Unilateral renal artery constriction frequently produces hypertension in the rat. If nephrectomy of the constricted kidney is performed within two to three weeks, the blood pressure usually returns to normal; if nephrectomy of the constricted kidney is performed after two to three months, the hypertension usually persists, presumably because of changes in the opposite kidney. Similar results have been reported for the rabbit. Unilateral renal artery constriction without contralateral nephrectomy exceptionally produces protracted hypertension in the dog and in such instances excision of the "constricted" kidney results in a prompt return of the blood pressure to normal. However, this experiment has not to my knowledge been performed in dogs hypertensive for more than six months. In a few instances, these findings have been applicable to man where nephrectomy has resulted in the cure of hypertension due to unilateral renal disease. Again, of course, such hypertension is, by definition, not essential hypertension.

(3) Various sympathetic blocking drugs have a temporary and irregular effect in decreasing the blood pressure level of renal hypertensive dogs, rats, and monkeys. The same is true for humans with essential hypertension.

(4) A very low salt diet reduces the blood pressure of an occasional dog with experimental renal hypertension and also significantly reduces the blood pressure of a 10 per cent minority of patients with essential hypertension.

(5) Certain marine and fish liver oils and fractions thereof have been found inconstantly to contain variable amounts of an orally effective antihypertensive principle. This principle is sometimes associated with vitamin A, but definitely is not vitamin A. The principle has shown antihypertensive effects in experimental renal hypertension in dogs and rats and in human essential hypertension. Presently, however, there are to my knowledge no active preparations of such marine and fish liver oils available even for limited experimental study.

(6) Curiously enough, the oral administration of the pressor amine, paredrine, to renal hypertensive dogs has an antihypertensive effect which begins after two to three weeks. Twenty-four chemically related amines have been shown to be without antihypertensive effect. More work remains to be done to determine the mechanism involved.

(7) Repeated courses of crude anterior pituitary extract intramuscularly have an antihypertensive effect in renal hypertensive dogs probably because of some type of antihormone or antibody effect. This finding suggests that the anterior pituitary-adrenal cortex axis is involved in the maintenance of experimental renal hypertension.

(8) Certain renal extracts believed to contain the so-called renal blood pressure regulating hormone have shown inconsistent effects in the treatment of experimental renal hypertension and essential hypertension. On the other hand, chronic renal hypertensive dogs can be successfully treated with daily intramuscular injections of crude hog renin and semi-purified hog renin over a period of 4-8 months or longer. The development of experimental renal hypertension in dogs following renal artery constriction can be prevented by prophylactic administration of hog renin and semi-purified hog renin for several months prior to constriction. These excellent therapeutic and prophylactic effects are highly correlated with the antirenin titre of the blood. There is also excellent evidence that antirenin (or a related antibody) produced by the injections of crude and semi-purified hog renins is capable of protecting against the blood pressure increase of experimental malignant hypertension in dogs. Likewise it has been shown that passive immunization with antirenin (or a related antibody or antibodies) is effective in reduc-

ing the blood pressures of experimental renal hypertensive dogs. Unfortunately this type of therapy with hog renin cannot be applied to man at present because antirenin to hog renin does not neutralize human renin. However, human renin is being collected for the production of antirenin to human renin in goats and horses. Later, the effect of passive immunization with purified antirenin to human renin on essential hypertension will be determined. Significant reductions in blood pressure by passive immunization with antirenin to human renin would suggest a renal, renin basis for the essential hypertension in such patients. If a significant percentage of patients with essential hypertension should prove by this technique to have their hypertension primarily or dominantly on a renal basis involving renin, passive administration of antirenin to human renin would be of some therapeutic value, but, what is more important, various research groups would be stimulated to alter the antibody producing properties of hog and other animal renins to overcome the species difference which presently precludes their trial in the treatment of essential hypertension.

Spontaneous (Essential?) Hypertension in the Dog

Our research group and others have established the range of the mean femoral blood pressure of normal dogs to be from 80 to 145 mm. Hg., a majority of dogs falling between averages of 110 and 130 mm. Hg. For a mean pressure of 80 mm. Hg. in the dog, the systolic pressure is likely to be 110 mm. Hg. and the diastolic 50 mm. If the mean pressure is 100 mm. Hg. in the dog, the systolic is likely to be 140 and the diastolic 60, which means that the pulse pressure is somewhat greater in the dog than it is in man. In general, the mean blood pressure variation for a given dog from day to day and week to week is approximately 20 mm. Hg., although some dogs show smaller variations and others show variations up to 40 mm. Hg. Conditions which influence the blood pressure of man similarly influence the blood pressure of the dog. Thus, new surroundings, unfair treatment, and other sources of nervous and emotional tension will elevate the blood pressure of the dog. As an example, the blood pressure of a dog will occasionally decrease by 20 to 40 mm. Hg. over a period of 2 to 3 months while the animal is acclimatizing to our Animal Hospital. Some dogs show a reduction of as much as 20 mm. Hg. in mean pressure during the warm summer months. The influences of sex and age on the blood pressure of the dog are less well-known than for man, although some of our observations suggest a very slow and gradual increase in blood pressure with advancing years in the dog as in the human.

Our laboratory and others have found that one dog in 100-150 consistently and persistently maintains a pressure level averaging 150 mm. Hg. or more. Perhaps the incidence of so-called spontaneous hypertension in the dog would be higher if more of the dogs seen in our laboratory were in the 8-12 year old group rather than the 1-4 year old group. Limited studies conducted on spontaneous hypertension in the dog suggest that this form of hypertension is quite similar to essential hypertension in man. Thus, these animals show renal blood flow, glomerular filtration rate, and tubular excretory mass within normal limits. This is likewise true for early essential hypertension in man. Clinical study and the usual laboratory examinations reveal no signs of abnormality in these spontaneous hypertensive dogs, except, of course, the increased systolic and diastolic blood pressures. The same is frequently true for early essential hypertension in man. Some investigators in this field have claimed that there is no such thing as spontaneous hypertension in the dog and when hypertension occurs in this species it is due to chronic glomerulonephritis or pyelonephritis. These conditions do occur in the dog and obviously may be accompanied by hypertension. However, the dogs which we have studied and similar hypertensive dogs which have been studied in other laboratories have shown no signs of chronic glomerulonephritis or pyelonephritis while under observation for as long as six years or, subsequently, at post-

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IMMUNOLOGIC APPROACHES TO THE CANCER PROBLEM

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Views regarding the value of immunologic studies in cancer research have fluctuated widely within the past fifty years. Reviewing the literature of these years, three periods become readily discernible. The *first*, beginning at the turn of the century, coincided with the dawn of modern experimental oncology. During this time, many investigators felt that immunologic approaches were most likely to yield results decisive for the understanding and conquest of cancer. The *second* period started between 1925 and 1930, and possibly found its clearest expression in the classic review of Woglom[1] on "Immunity to Transplantable Tumors". This period, which gradually and almost imperceptibly came to an end in the early forties, could superficially be characterized by the negative feature of disappointment, motivated by the lack of accomplishments of immunologic studies during a quarter of a century and the life time of many a research worker. With much greater justification, this period of barely twenty years should be singled out as one in which fundamental contributions were made to cancer research in the fields of carcinogenesis, metabolism, genetics, endocrinology, and nutrition. The *third* period is the present, hardly more than ten years in existence, and exhibiting a reversal of the trend — renewed interest in, and more frequent use of, immunologic ideas and methods in experimental oncology.

It may be worthwhile to briefly examine the reasons for these diametrically opposed attitudes toward the role of immunology in cancer research. In this writer's opinion, the earlier preoccupation with, as well as the subsequent apparent failure of, immunologic oncology was the result of expectations going far beyond possible realization. An analogy was drawn between neoplasia and infectious diseases. It was in the latter field that immunologic and serologic work achieved such impressive results in the first decades of this century. Applying these same methods, workers engaged in immunologic studies aimed directly and specifically at finding answers for the three crucial problems of cancer: cause, diagnosis, and cure. One need not dwell on the obvious fact that these goals were not reached. Nevertheless, the extensive data accumulated in the course of these studies, when subjected to critical appraisal[1], led to the recognition of important principles which put future work on a much sounder basis. A great number of earlier studies on tumor immunity in animals were invalidated because of neglect of genetic differences between different strains, or because of the employment of heterozygous animals. Serologic studies often were found to be vitiated by inadequacy of technic. Therapeutic trials with supposedly specific tumor antiserums all too frequently were poorly sampled and controlled, and if used clinically, did not take into account the vagaries of human neoplastic disease.

Resumption of immunologic studies of cancer within the last ten to fifteen years was accompanied, for the most part, by a full realization of these pitfalls and stumbling blocks. At the same time, it was facilitated and stimulated by progress made in immunochemistry, serologic technics, availability of genetically pure animal strains, and advances made in general oncology. On the whole, the approaches were of a more fundamental nature and did not *a priori* aim at results of practical applicability.

Comprehensive reviews of immunologic studies on cancer have been presented on previous occasions by Woglom[1], Spencer[2], and Stern and Willheim[3]. The most recent and up-to-date survey of this field is that by Hauschka[4]. This presentation will not attempt any such inclusive coverage, but rather will deal with selected approaches and trends that have either furnished us with new facts

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on cancer or seem to point to possible new ways of looking at the neoplastic process.

I. Antigenic Structure of Tumors and Tumor Agents

The most crucial and fundamental question of tumor immunology is obviously that of the existence of tumor-specific antigens. Actually, this constitutes three questions: (1) Is it possible to demonstrate that neoplasms contain antigens qualitatively different from those present in the normal tissue of the host? (2) If so, are the same "abnormal" antigens present in all malignant tumors, or are there different "tumor antigens" specific for each species and/or for each tumor type? (3) If the answer to the first question is to the negative, is this a reflection of the true state of affairs, or might it merely mirror the limitations of our presently available methods? Is it, so to speak, an inability to detect antigenic differences because tumors are too much "flesh of our own flesh"?

To date, none of these questions has been unequivocally answered. Regarding the first question, there is a respectable and convincing body of data, derived from experiments of tumor transplantation in animals, especially mice, in which a close relationship was demonstrated between normal tissue antigens and neoplastic antigens. Genes referred to as *histocompatibility genes*[5,6] were shown to determine the presence of these antigens in a manner similar to that known to operate in human blood factors. As a matter of fact, some of the tumor antigens were found by Gorer[7,8] to be present also in erythrocytes of the identical strain in which the tumor developed. Successful tumor transplantation, as a rule, is possible only if there is concordance between the antigens present in the tumor and in the transplant host. If the transplanted tumor contains antigens absent in the new host, the inoculum either does not "take" at all, or regresses after initial growth. Serum of animals in which such tumors have regressed was found to contain, in some instances, agglutinins for red cells of the strain of origin of the transplanted tumor[8].

A number of recent investigations have employed methods of differential centrifugation of cell homogenates in order to study the immunologic properties of the most important cellular fractions: nuclei, mitochondria, microsomes, and nonsedimentable cytoplasmic constituents. In this manner, Dulaney and associates[9] studied cell fractions of normal and leukemic spleens. The cytoplasmic fractions, especially the mitochondria and microsomes, were found to contain species-specific, organ-specific, and cell fraction-specific antigens. In addition, Forssman antigen was found to be present, particularly in the small particle fractions (mitochondria and microsomes). The reactivity of antiserum produced against fractions of leukemic cells exceeded that of antiserums against homologous fractions of normal splenic cells. However, the authors found no evidence proving that the difference depended on qualitative rather than quantitative changes in the antigens. In other words, neoplastic cell fractions apparently were more active because they were richer in the same antigenic material also present in normal tissue. Comparison of nuclear and cytoplasmic fractions showed superior antigenic activity of cytoplasmic derivatives from both normal and neoplastic tissue, again without any specificity of neoplastic antigens[10]. A similar conclusion, namely failure to prove the presence of tumor-specific antigens, was drawn from their work by Malmgren and associates[11,12]. These authors tested serologic properties of mitochondria isolated from normal and neoplastic mouse tissues. Mitochondria of mouse hepatoma were found to be more closely related to mitochondria of normal mouse liver than to those prepared from mouse mammary cancer[11]. This is in contrast to other biochemical properties of tumors, *e.g.*, the similar enzymatic pattern toward which all tumors were found to converge as compared with their normal matrices[13]. In further investigations, stronger reactivity in complement-fixation tests was observed with antiserums against homologous cell fractions of homologous neoplastic tissues. However, quantitative differences were assumed to be able to account for these findings, negating any necessity to postulate qualitative anti-

genic differences. In these studies, as well as in those of Davidsohn and Stern[14], older reports on the presence of Forssman antigen in mouse tumors were corroborated. This antigen is shared by certain normal and neoplastic mouse tissues. Microsomes and mitochondria were found to exceed other cell fractions in content of Forssman antigen. Mouse strains that differ regarding the presence of natural agglutinins for sheep red cells in their serum were not found to be distinguishable from each other by presence of Forssman and Forssman-like antigens[14].

Maculla[15-17] investigated the antigenic pattern of several transplantable mouse tumors, comparing nucleoprotein, protein, and cytoplasmic fractions with homologous material from fetal and adult normal mouse tissues. A considerable cross-reactivity of some neoplastic and fetal antigens was detectable, and tumor nucleoproteins appeared to be distinguishable from their normal counterparts. Extensive studies on the antigenic specificity of rabbit Brown-Pearce carcinoma were carried out by Kidd[18] and associates. According to these authors, the rabbit tumor contained antigens absent in normal rabbit tissue as well as in other rabbit carcinomas. Hauschka[4], in his recent review, pointed to the possibility that slight isoantigenic differences might account for these findings because the tumor investigated arose originally in a hybrid rabbit and because the serologic reactivity of the Brown-Pearce antigen was more clearly demonstrable in some rabbit lines than in others. Furthermore, it is of interest that the Brown-Pearce tumor antigen was not found in other rabbit tumors, a fact indicating serologic specificity differentiating tumors of the same species.

A different picture is presented by those investigations which dealt with known tumor agents of viral or related nature. Such studies demonstrated antigenic specificity of viruses of filtrable fowl tumors, especially the Rous sarcoma[19], of the virus of Shope rabbit papillomas[20.21], and of the milk agent ("mammary tumor inciter") in mice. The latter agent has been known, since the fundamental work of Bittner[22,23], to be one of the determining factors in the development of breast cancer in mice. Antigenic specificity of this milk agent was suggested by the results of several workers who injected mouse tissues or extracts containing the milk agent into rabbits or guinea-pigs[24-26]. Neutralizing antibodies, inhibiting the growth of mammary tumors, were obtained in some experiments. On the other hand, Law and Malmgren[27] failed to find evidence for qualitative serologic and immunologic differences when testing mouse tissues of the same strain with and without the milk agent. In recent work, Heidelberger, Graff, and Haagensen [28] injected rabbits with highly purified preparations of the milk agent isolated from the milk of a strain known to carry the agent (RIII). The antiserum so produced reacted strongly with the homologous antigen, but showed only little cross-reactivity with an analogous milk fraction obtained from C57 Black mice known to be devoid of the milk agent. The authors concluded that the milk agent is strongly antigenic and probably differs antigenically from other mouse tissue and milk proteins. The latter assumption requires further investigation. In spite of the antigenicity of the milk agent in foreign species, attempts to demonstrate neutralizing antibodies in mice have so far yielded negative results[29].

Before concluding the discussion of this aspect of immunologic cancer research, brief mention should be made of some hypotheses which correlate antigenic structure with the neoplastic process. Greene[30], on the basis of extensive experimental work, proposed the concept that malignant tumors differ from each other with regard to their "autonomy". This is a biologic property independent of morphologic features, which can be determined by the success of heterotransplantation of a tumor (conventionally into the anterior chamber of the guinea pig eye). This "autonomy", as a rule, is gradually acquired by the tumor. One of the factors that may be responsible for the development of tumor autonomy is the loss of antigens by the tumor[31]. This decreases the chances of stimulating production of antibodies in the alien species used for the heterotransplantation. Actually, shifts in the

antigenic structure of transplanted tumors have been observed[4]. Some mouse tumors, such as sarcoma 180, can be successfully transplanted into mouse strains of diverse genetic constitution. This might be taken as an indication of the lack of certain antigens in this tumor.

On the other hand, new antigens might arise in neoplasms on the basis of *gene mutation*. Levine, *et al.*[32] recently reported the case of a patient with gastric carcinoma who was found to have in her serum an isoantibody reacting with all human erythrocytes except her own and those of her sister. From this he concluded that the patient and her sister lacked a certain blood factor (TJ^a) present in the overwhelming majority of human red cells and that her isosensitization was the result of the presence of the antigen in her gastric tumor. Since the presence or absence of the red cell antigen is determined genetically, Levine assumed that the presence of the antigen in the tumor was indicative of a somatic mutation — a process which has often been considered to be connected with, or responsible for, tumor development.

II. Serologic Cancer Tests

The complex theoretical aspects of the specificity of cancer antigens and antibodies discussed in the preceding section have not deterred a number of investigators from attempting to develop serologic methods for the diagnosis of neoplastic disease. Penn[33] recently reported the successful use of an unsaponifiable lipid extract prepared from human metastatic liver carcinoma in a flocculation test. The specificity and sensitivity were claimed to be high enough for practical application. Subsequently, the same author[34] substituted bile steroids for the liver extract, with satisfactory results. Final evaluation of this test must await reinvestigation by other workers.

A precipitation test of alleged diagnostic value was proposed some time ago by Gruskin[35]. It consisted of layering an alcoholic solution of an "antigen" prepared from fetal calf liver over the serum. A recent reinvestigation of this test yielded almost 95% positive results in 273 cancer patients, but 45% "false positive" results were obtained in cancer-free persons[36]. Use of alcohol itself, without the "antigen", gave results similar to those just mentioned. These findings confirm earlier observations[37], according to which many supposedly immunologic cancer tests actually reflect physicochemical deviations in the serum of cancer patients, resulting in a greater "lability" of proteins and other serum colloids.

Within the last years, Kahn[38] reported a large body of data on the "universal serologic reaction" (USR) derived from precipitation of serum with lipid antigen in varying concentrations of sodium chloride and at different temperatures. Patterns differing from species to species, and also between individuals of the same species were observed. Characteristic changes in the pattern of precipitation were associated with certain diseases, especially syphilis, yaws, and leprosy, but also, to a lesser degree, malaria and tuberculosis. No diagnostic patterns of the USR were noted in cancer patients[39,40] or in tumor-bearing mice[40]. The results were not affected by the choice of antigen. The opinion was expressed that the patterns observed were probably due to "increased wear and tear of tissues in general rather than the formation or release of any lipid specific for cancer"[40]. One group reported that in two-thirds of cancer patients repeatedly tested, an increase in the precipitation paralleled clinical improvement, and *vice versa*[39]. This observation is similar to that of Kahn and associates[41] who found changes of prognostic value in precipitation patterns after irradiation of cancer patients.

Complement fixation tests might be considered to be free of some of the unspecific physicochemical effects occasionally associated with precipitation and flocculation tests. However, Maltaner[42] has recently pointed out serious sources of error inherent in complement-fixation tests when used in experimental work: the anticomplementary activity of antigens containing thromboplastic lipids (cephalin) and the anticomplementary activity of serum, which is especially high in the rabbit. Since, after immunization with various antigens, the anticomplementary activity of rabbit serum was found to rise, misleading results may

be obtained unless proper precautions in technic are observed.

The effectiveness of complement-fixation tests has been investigated in rabbits with Brown-Pearce carcinoma. Positive reactions with a saline tumor extract were obtained two weeks after inoculation of heavy tumor suspensions, which was shortly after the tumors became palpable. Six weeks later, positive results rose to 84 per cent. Correct negative results of complement-fixation tests were found when extracts of Brown-Pearce carcinoma or of normal rabbit tissue were used with serums of normal rabbits or of animals injected with turpentine[43]. Significantly, the reactions in the complement-fixation test varied with the breed of rabbits used and hence involvement of isoantigenic differences cannot be excluded.

III. Inhibition of Tumors by Immunologic Methods

Adhering to classic immunologic concepts, one should divide efforts to inhibit neoplasms immunologically into those employing active immunity and those connected with passive immunity. In the first instance, protective or cytotoxic antibodies are expected to develop in the tumor host himself; whereas the latter type of immunity involves passive transfer of antibodies produced by a different individual of the same or a foreign species. Actually, the immunologic phenomena responsible for the results of some of these experiments are so incompletely understood that there seems to be little justification for classifying them rigidly. The most serious difficulty in interpreting most of this work lies again in excluding the possibility that tumor-inhibiting or tumor-protecting antibodies are in reality directed against isoantigens (differentiating strains or individuals of the same species, if methods of "active immunization" are used) or against species-specific antigens (if heterologous antibody is transferred passively).

A number of recent studies might be classified as attempts to demonstrate the development of "active tumor immunity" in animals. In a series of investigations, Lewis and co-workers[44-46] produced regressions of sarcomas growing in rats and found the animals resistant to challenge with a second transplant. Regression of the sarcomas was induced by injecting into the tumors alcoholic tumor extracts prepared from either rat sarcomas or from human carcinomas. In the latter instance, the percentage of regression of rat tumors was smaller than when homologous tumor extracts were used[44]. The immunity toward subsequent tumor transplants apparently required absorption of substances formed by the regressing tumors. Removal of an actively growing tumor which had not shown prior regressive changes produced no such immunity, but atrophy of tumors induced by depriving them of adequate blood supply was effective[45]. Similarly, when rats were transplanted with sarcomas in which ischemia had led to regressive changes, no growth of the inoculum ensued. However, the inoculated rats also became immune to subsequent transplantation of viable sarcoma[46]. Goldfeder[47] found that *in vitro* irradiation of rat lymphosarcoma at a certain level of exposure destroyed the growth potentiality of the tumor. Rats transplanted with irradiated tumor remained refractory to subsequent re-inoculation of non-irradiated tumor. She obtained similar results with the inoculation of mouse sarcoma 180 into heterozygous Swiss mice[48]. However, since an analogous procedure did not confer immunity on inbred mice injected with irradiated mammary carcinoma indigenous to the strain[49], one must assume that subtle isoantigenic differences were, at least in part, responsible for the immunity produced in the previously described experiments.

Regression of a certain percentage of lymphosarcomas C3H-ED growing in mice of the strain of origin (C3H) was achieved by severe riboflavin deficiency[50], intensive treatment with A-methopterin[51], inoculation of subthreshold amounts of tumors into the tail, and interference with the blood supply of the growing tumors[52]. In all these instances, mice in which the original tumor had regressed were found to be immune on re-transplantation of the tumor.

In another group of investigations,

antibodies produced in heterologous species were tested for their effect on tumor development and growth. Nettleship[53] injected rabbits with protein and nucleoprotein fractions of a rat lymphosarcoma. When lymphosarcoma-bearing rats were treated with these antiserums, retardation of tumor growth or regression of tumors was observed. The effectiveness of the antiserum *in vivo* paralleled its titer as determined by *in vitro* precipitin tests. Dulaney and Arnesen[54] immunized rabbits with various fractions of normal and leukemic mouse spleen. Cell suspensions of a transmissible mouse leukemia, when incubated with the rabbit antiserum prior to inoculation, failed to produce leukemia; anti-leukemic spleen rabbit serum was more effective in this respect than anti-normal-spleen serum, that is, cytotoxic activity was detectable in higher dilutions of the former serum. Mention has been made previously of antiserums prepared against the milk agent of the mouse. In some of these studies[24-26], the antiserums were found to inactivate the milk agent also *in vivo*. Extremely well controlled experiments along these lines were recently caried out by Law and Malmgren[27]. These authors injected rabbits with normal lactating mouse mammary glands or with mammary carcinoma originated in mice of the same inbred strains. Tissues were derived from mice with and without the milk agent. Thus, four types of antiserums were obtained, depending on the antigen used: (1) normal breast tissue with milk agent; (2) and without milk agent; (3) mammary carcinoma with milk agent; (4) and without milk agent. Since no consistent differences in the cytotoxic effects of these antiserums were observed, it is unlikely that antibodies specific for the milk agent and/or for the tumor were operative.

A novel approach to immunology of cancer was selected by Creech[55]. With his collaborators, he prepared protein conjugates of carcinogenic compounds such as dibenzanthracene and dimethylaminostilbene. In accord with the fundamental observations of Landsteiner[56], antiserums against the carcinogen-protein conjugates showed, *in vitro*, specific reactivity with the conjugate as well as with the prosthetic group, *i.e.*, the carcinogen. Some cross-reactivity occurred, as was to be expected, between hydrocarbons of related chemical structure, such as 1,2-dibenzanthracene and 3,4-benzpyrene. *In vivo*, the purified protein-carcinogen conjugates showed no carcinogenic activity. Further work is under way in order to test whether (a) it is possible to produce adequate levels of antibodies to the conjugates in animals susceptible to carcinogens; and (b) if such measures will protect the immunized animals against the carcinogenic activity of the compound incorporated in the conjugate.

IV. Resistance and Susceptibility to Tumors

Anybody who has met with the problems of human cancer more than casually and has experienced the unpredictability of this disease, will find it difficult to avoid using the terms "resistance" and "susceptibility" in connection with neoplastic disease. A recent report relating clinical experiences, such as temporary arrest of tumor growth and long dormancy before reoccurrence or before metastases, re-emphasized the need for postulating "natural resistance" to cancer and concluded that the question". . . is not what makes the cells suddenly grow but what has held them in abeyance for so long"[57]. *Vice versa*, the occurrence of multiple tumors with a frequency exceeding statistical chance makes one suspect the existence of some factors responsible for increased susceptibility to neoplasia. Results of animal experimentation, in spite of being much better controlled, fit in well with clinical experience. True, certain factors of resistance and susceptibility have been clarified in experimental oncology and were identified as genetic, hormonal, metabolic, or dietary factors. Nevertheless, a considerable "insoluble residue" of ignorance has so far resisted identification. Obviously, immunologic approaches should be among those selected for attacking these problems.

The resistance to tumor growth based on species or strain differences between the donor and the recipient of the tumor implants has formed the basis of numerous investigations. As mentioned in pre-

vious sections, even slight isoantigenic differences have been found capable of producing immunity to tumors. A sarcoma which originally arose in mouse strain DBA was readily transplantable into mice of strain C. However, if defibrinated blood or a small amount of washed erythrocytes of strain DBA was injected into C mice prior to tumor inoculation, resistance to this tumor was induced[58,59]. Other normal tissues, like spleen or lymph node, have been used to protect mice against the subsequent growth of a lymphosarcoma indigenous to the strain. Spleen and lymph nodes were derived from various strains—even from sublines of the strain of origin in which the tumor grew fatally[60]. Hence, even slight antigenic differences between sublines may be capable of inducing resistance.

Resistance and susceptibility to tumors apparently are influenced by qualitative as well as by quantitative factors. Snell, Kaliss, and collaborators[61-63] reported that enhancement or inhibition of tumor growth ensued after mice were pretreated with injections of lyophilized tumor. The results depended on the host strain, the type of tumor, the dosage of pretreatment, and the combination of all factors[61]. Neoplastic as well as normal tissues of mice exhibited this property[62]. Further analysis showed that survival of tumor homoiografts (transplants of mouse tumors into strains other than the strain of origin) was enhanced if large doses of lyophilized tumor or normal tissue preceded tumor inoculation, whereas small doses speeded regression of tumors[63]. Snell[64], reviewing this work and that of other authors suggested that this phenomenon might be related to observations by Felton[65] on "immunologic paralysis" in mice treated with large doses of pneumococcus polysaccharide. Protective antibodies were produced in mice treated with small doses of polysaccharide, but large doses had the opposite effect. Tumor growth-enhancing properties of tumor extracts have been studied in a long series of investigations by Casey[66,67]. This author demonstrated such effects with extracts of tumors and normal tissues—with the agent ("XYZ factor") exhibiting species-specificity. The assumption of isoantigenic differences cannot account for this effect, since, in recent work, the XYZ agent was also found in mouse tumors used for pretreament of animals of the identical strain[68].

Within the last years, the influence of adrenocortical hormones on immunologic phenomena has been repeatedly studied. The growth of a mouse lymphosarcoma in mice of different genetic lineage was found to be enhanced after pretreatment of the animals with cortisone. The hormone also prevented the development of resistance which otherwise followed treatment of mice with splenic and lymphatic tissue[60]—and lymphosarcoma growth proceeded as in untreated animals. On the other hand, "immunity" already established in mice, *e.g.*, following the regression of a tumor, was not abolished by cortisone. Hence, the hormone may be assumed to depress antibody formation rather than to interfere with the effect of antibodies previously produced[69]. The barrier of strain or even species difference frequently does not prevent tumor growth when inoculation is made in the anterior chamber of the eye, *e.g.*, of the guinea pig. Eichwald and co-workers[70] concluded that failure of growth after subcutaneous tumor inoculation demonstrated "natural resistance" of the host, whereas failure of growth or regression after initial growth of the intraocular transplant was based on acquired immunity.

Ionizing radiation has been shown to affect tumor resistance. Hoch-Ligeti[71] studied the effect of x-radiation on the development of hepatomas in rats fed the carcinogen p-dimethyl aminoazobenzene. Small doses of "soft" radiation applied to the skin of the back and hepatic region decreased the incidence of tumors, whereas higher doses of more penetrating radiation had no such effect. The author assumed that this effect depended partly on the stimulation of reticulo-endothelial tissues, expressed in proliferation of Kupffer cells, and partly on hormonal mechanisms, indicated by the adrenal enlargement seen in irradiated animals. Cohen and Cohen[72] were able to destroy resistance of rats to transplanted hepatoma by preceding total

body irradiation. Since the injection of trypan blue had a similar effect, both forms of intervention may be assumed to have interfered with tumor resistance of the hosts by impairing reticulo-endothelial function.

V. Immunologic Response in Neoplasia

Some of the findings discussed in the preceding section, as well as other data derived from a wide range of clinical and experimental observations, suggest that reticulo-endothelial activity may be a factor in "resistance" to cancer[73,74]. It is therefore of considerable interest that changes in the immunologic response, which in itself is closely connected with reticulo-endothelial function, have been shown to be associated with some neoplastic processes.

Depression of antibody formation in patients with leukemia or lymphomas was reported many years ago by several authors who found negative Widal reactions in leukemic patients with typhoid fever or after typhoid vaccination[75,76] and who failed to detect agglutinins for sheep erythrocytes after the injection of horse serum[77]. Low titers of isoagglutinins were noted in most patients with chronic leukemia[78,79]. Davidsohn[80] confirmed these findings and observed, in acute leukemia and after x-ray treatment of chronic leukemia patients, normal or even slightly elevated titers. More recently, Evans[81] demonstrated a depressed antibody response to typhoid vaccine in patients with lymphomas and leukemias, but not in patients with other malignant tumors. Immunization with pneumococcal polysaccharides was used by Larson[82] with the following results: little or no antibody formation in chronic lymphocytic leukemia and multiple myeloma; slightly higher than normal antibody levels in chronic granulocytic leukemia; and exceedingly high antibody production in acute leukemia. The latter response could be suppressed by cortisone.

Dubin[83] concluded, on the basis of earlier reports and his own investigations, that patients with Hodgkin's disease exhibit poor immunologic response. Hoffman and Rottino[84] reported that patients with Hodgkin's disease were capable of producing typhoid agglutinins, but those with advanced disease were unable to maintain agglutinin levels for more than three months. The same authors[85] confirmed earlier findings on the presence of an anergic state to tuberculin in the majority of patients with Hodgkin's disease.

Interesting data were recently presented regarding agglutinins for Proteus OX19. Eighty per cent of normal persons or patients with non-neoplastic disease showed the presence of these antibodies. But, they were absent in over 70 per cent of cancer patients[86].

Results of animal experimentation fit in well with these clinical observations. Lowered immune response to egg albumin and sheep cells was reported in mice with spontaneous and transplanted tumor[87, 88]. A considerable depression of immune hemolysin for sheep and chicken red cells was observed in leukemic mice[89,90]. The presence of transplanted tumors and the administration of carcinogens (methylcholanthrene, dibenzanthracene, butter yellow), as well as of antitumoral agents (Guanazolo, A-methopterin, colchicine, triethylene melamine, urethane), depressed titers of immune sheep hemolysin in mice[91-93]. The assumption that the lower antibody levels in leukemic or tumor-bearing animals are the result of accelerated metabolic degradation of serum proteins, including immune globulin[88], was not borne out in other studies[91-94]. "Natural" agglutinins for Proteus OX19 present in chicken serum disappeared in animals with growing Rous sarcomas[95]. The bactericidal power of serum for E. coli and S. typhosa was found to be reduced in tumor-bearing animals[96]. Animals with tumors were stated to be more susceptible to bacterial infection, and this was surmised to be a reflection of depressed immunologic reactivity[97].

Studies carried out in our laboratory showed that the occurrence and titer of natural heterohemagglutinins, such as agglutinins for sheep and chicken erythrocytes, differ considerably and consistently in twelve inbred mouse strains[98-101]. Genetic factors were found to determine, at least in part, the presence and titers of these antibodies.

Hence, antibody determinations may prove helpful as a method of testing for homozygosity in mice and possibly other species[102]. No correlation was found between natural hemoantibodies and the rate of spontaneous incidence of mammary or other tumors in the strains tested. Levels of immune hemoantibodies, determined after injection of mice with sheep or chicken red cells, again were characteristic for each individual inbred strain, but differed from one strain to the other. Preliminary analysis of immune hemoantibodies in mice of nine inbred strains indicates that, with one exception, mice of strains with low spontaneous tumor incidence exceed in their immunologic response animals of strains with high spontaneous tumor incidence[103]. Although definitive evaluation of these findings would be premature, the observations made by several groups of investigators and by us suggest that further studies on immunologic response in neoplasia may contribute to a better understanding of the tumor-host relationship.

Conclusions

An attempt was made to survey and evaluate recent investigations in which immunologic concepts, methods, and interpretations were applied to experimental oncology. These studies included antigenic structure of tumors, serologic cancer diagnosis, tumor-inhibiting antibodies, resistance to cancer, and immunologic response in neoplasia.

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CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. E. B. FREILICH, Chairman DR. I. DAVIDSOHN, Secretary

Abstracted by DR. DONALD R. RUSS

A 56 year old white male was admitted to Mount Sinai Hospital on March 9, 1951. He had apparently been well until one week prior to admission when he experienced a few chills, fever, and shortness of breath. The patient had a past history of cough for many years. The cough had become increasingly severe during this week and the sputum had become blood tinged. He had also had some night sweats. There had been no evidence of tuberculosis. He had had rheumatoid arthritis for several years.

Physical examination: The blood pressure was 130/70 and the pulse was 100. There was moderate pallor. The tonsils were slightly enlarged. There were palpable, enlarged, and non-tender cervical, axillary, and inguinal lymph nodes. There were crepitant rales at both lung bases. There was an apical systolic murmur. The liver was palpable 5-6 cm. below the costal margin. There were a few petechial hemorrhages in the oral mucosa and over both tibias. While in the hospital, the patient received blood transfusions. He ran a steadily downhill course which was occasionally febrile. The fever, however, was easily controlled with penicillin. The lymph nodes steadily increased in size. For several days before death, the patient had difficulty in breathing and was placed in an oxygen tent—with little benefit. Terminally, there was a large amount of diffuse petechial hemorrhage. He died on March 29, 1951.

Dr. A. Samuels, Internist: This 56 year old white male was apparently well until the first week in March 1951, when I saw him for the first time. He had developed at this time what we thought was an upper respiratory infection with fever, dyspnea, and hoarseness. At first, with this impression, I gave him treatment with penicillin. It was soon apparent that he was not responding. Because of the increased severity of his symptoms and marked toxicity, the patient was hospitalized. At this time, because of the progression of the disease, I thought of a somewhat atypical bilateral bronchopneumonia. Physically, at this time, he showed some enlargement of both axillary and inguinal lymph nodes, and the liver was palpable. The petechiae were first noted on the day following admission. There were only a few over the tibias and in the oral mucosa.

Upon his admission, we found, in the peripheral blood, large numbers of immature blood cells. The clinical picture of leukemia began to develop. The lymph node enlargement and petechial hemorrhages became prominent. The tonsils also enlarged markedly. On March 13 the patient had chills and a fever of 103° F.

We treated him with repeated transfusions, but his course was steadily downhill. Our diagnoses were: (1) acute leukemia, (2) thrombocytopenia due to the leukemia, and (3) leukemic infiltration of both lungs.

Dr. B. Kavka, Roentgenologist: We examined the chest three days after admission. The x-ray showed an area of increased density in the left hilar region extending down to the region of the lingular lobe of the left upper lobe. This is not specific when it appears on a single film. It may represent an infiltration from pneumonitis or it may represent a vascular engorgement. With the history in this case of a very high white count we could consider a leukemic infiltration. The cardiac silhouette shows the transverse diameter at the upper limits of normal, and the aortic knob is slightly prominent. The lower borders of some of the ribs on the right are a little radiolucent, suggesting a notching, but this is not specific in appearance. In view of the history, it would be interesting if we knew if there was any leukemic infiltration of the bony structure. In general, the bony structure as shown here is within normal limits. The left apex is more dense than the right, which may

be soft tissue. There is no evidence of calcification. On a single film, however, we cannot consider this as evidence of tuberculosis. To rule out such a lesion it would have been advisable to take an apical view. In summary, this is a pneumonitis of the left hilar region, which, in view of the history and the clinical findings, may represent leukemic infiltration.

Postmortem Findings and Discussion

Dr. I. Davidsohn, Pathologist: This patient presented, at the time of his stay in the hospital, no diagnostic problem. It was obvious that the patient had acute leukemia. The matter of classification is another problem, which we will discuss later.

One cannot place acute leukemia in a particular pigeon-hole, but this is not extremely important for the clinician. There are, however, a few things which are interesting in this case. One is the extremely rapid course. According to the history, this patient was ill only four weeks. He was here in the hospital about twenty days, from the 9th to the 29th of March, and according to the history he had been ill only one week prior to admission. Of course, fulminant cases of acute leukemia are known to occur — cases in which the duration of the illness from the beginning to the fatal outcome is only a few days. It is interesting to compare this history of four weeks with what we found at autopsy. One always wonders how to treat such a case. Sturgis says: "There are only two types of treatment which might be helpful and they should be given a trial. One is the use of repeated blood transfusions. These should be given in amounts of 500 cc. at daily intervals or every other day as indicated. They produce beneficial effects by combating the anemia and controlling to some extent certain patients with tendency to bleed." The other treatment that he refers to is the use of antibiotics. He does not, even in 1948, refer to the use of some of the other chemotherapeutic agents and we are not so sure that they are helpful in the adult. I wanted to point out that, as recently as 1948, blood transfusions were still given the first place of importance in the alleviation of some manifestations of acute leukemia, and that the author, a recognized authority on the subject, says 500 cc. should be given daily or every other day as indicated. I have been interested for a long time in the origin of the idea that one should give 500 cc. to a patient. Why 500 cc.? It is a purely arbitrary recommendation and in my opinion it leads to a tremendous waste of good blood. I am very much in favor of blood transfusions in the treatment of acute leukemia because I have seen, and others have seen and reported, results in some cases which were as good as those, for instance, with folic acid antagonists. In some cases, the results are remarkable. Therefore, I would like to analyze this case.

Note that the red blood counts on the 10th, 12th and 14th were about the same, approximately 2.5 million, and that the hemoglobin was about 8 gm. The patient was given blood transfusions of 500 cc. each on the 14th, 15th, 16th, and 17th. Beginning with the 15th, the red count increased; it is 2.9, 3, and 3.6 million. The patient was then given two transfusions of 250 cc. each and the blood count at that time went up to almost 4 million (3,880,000). At this time, after consultation with the doctor, it was decided to reduce the amount of blood given. From then on, for the last 10 days of the patient's life, he received nine transfusions of only 150 cc. each. The patient received altogether 3350 cc. of blood in the period of three weeks. In the first period, between the 14th and 19th of March, when he had five transfusions with an average of 500 cc. per day, his red count went up from an original of 2.5 million to 3.8 million and his hemoglobin went up to 11.4 gm. During the second period, when he was much sicker than at first, he was receiving only 150 cc. and yet you will notice that the red count and hemoglobin were maintained at optimum level. In other words, with a total of 1,350 cc. during a period of 10 days, it was possible to maintain a red count level at least as good as that during the previous five days when he received altogether 2,000 cc. I want to make the point that the idea of giving 500 cc. of blood each day is entirely unrealistic, because the body cannot handle

LABORATORY DATA

Blood Count:	RBC (mill.)	Hb. (Gm.)	C.I.	WBC	Differential Count							Platelets
					Blast.	Myelo.	Meta.	Stabs	Segs	Lymph	Mono	
3/10/51	2.5	8.0	1.02	18,900	90%			1.0%	3.0%	6.0%		
3/12/51	2.48	7.8	1.00	37,000	72		1.0%	7.0	2.0	18.0		19,000
3/14/51	2.55	8.5	1.02	38,000	79	1.0%	1.0	3.0	1.0	12.0	3.0%	
3/15/51	2.9	9.5	1.05	53,500	89	1.0	1.0	2.0		4.0		40,000
3/16/51	3.09	10.1	1.05	54,400	80	4.0	2.0	3.0	1.0	4.0	6.0	
3/17/51	3.6	11.5	1.02	46,600	88	0.3	0.1	1.7		8.6	2.4	30,000
3/19/51	4.0	13.2	1.05	35,700	91	1.6	0.6	1.4	0.4	4.1	0.9	
3/20/51	3.88	12.1	1.00	56,000	96	0.2	0.2	0.6	0.2	2.8		23,000
3/21/51	4.1	12.8	1.00	45,900	91	3.5	0.4	0.3		4.0		
3/22/51	3.91	12.3	1.01	47,000	92	1.5		2.5		4.0		48, 000
3/23/51	4.01	12.3	0.98	44,600	86	3.0		1.5	0.5	8.0	2.0	
3/24/51	4.5	14.2	1.00	43,800	90	1.2	0.4	0.2	0.4	5.0	0.6	
3/26/51	4.56	14.4	1.01	31,500	84	5.0	1.0			7.0	2.6	57,000
3/27/51	3.79	12.1	1.03	39,300								39,000
3/28/51	3.81	12.3	1.03	55,300	95	4.0			0.2	4.0	0.8	
3/29/51	3.49	11.1	1.03	200,000	98	0.4		0.4		1.2		21,000

Several plasma and reticulum cells were seen on almost every smear.
Nucleated red blood cells (1-3/100 WBC) were seen on several occasions.
40 and 30 smudge cells were noted, respectively, on 3/23 and 3/29.

	Coagulation Time	Bleeding Time	Clot Retraction Begin	Clot Retraction Complete	Hematocrit	Sedimentation Rate, Corrected
3/12/51	7 minutes	3 minutes	1 hour	4 hours	26	20
3/20/51	5 "	3 "				
3/27/51	7 "	3 "	incomplete			

Blood transfusions: 500 cc. given on 3/14, 15, 16, 17/51
250 cc. given on 3/18, 19/51
150 cc. given on 3/20, 21, 22, 23, 24, 25, 26, 28, 29/51

Blood Chemistry:	Sugar	Urea Nitrogen	Uric Acid
3/10/51	73 mg%	30.2 mg%	
3/12/51	98 mg%	17.6 mg%	
3/13/51			4.5 mg%

Urinalyses:	Reaction	Sp. Gravity	WBC	RBC	Sugar	Albumin	Bacteria	Casts	Crystals
3/10/51	5.5	1.019	2-3	0	0	+	+	0	0
3/22/51	5.0	1.013	2-4	0	0	0	yeast	-	uric acid

Sputum: 3/10/51 No acid fast bacilli seen.

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this quantity. We lose or destroy normally about 1 per cent of our red cells each day. Therefore, we determine the approximate weight of the patient and divide it by 10 or 12 to get the total blood volume, and in this way calculate how much is necessary to replace the usual 1 per cent loss.

You will see later that this patient probably did not produce one red blood cell during his stay in the hospital. Therefore, in order to give him what he needed, the transfusions were reduced to approximately 150 cc. This probably is a little in excess of what he used, but we must compensate for some hemolytic factor which is present in most cases of acute leukemia. We do not know what it did for him, but the good effect on the blood count was much more economically achieved with an average of two individual transfusions of 250 cc., for a total of the same 500 cc.

One may think that if we had given him 500 cc. twice instead of smaller frequent transfusions of the same amount,

the same level would have been maintained. I have reason to believe from my experience that that is not the case. I believe that it is more beneficial to the patient, and certainly more economical, to administer the blood in smaller but more frequent transfusions. In cases such as this, it is also best to place the marrow at rest, which may possibly be accomplished by giving small, frequent transfusions — just enough to maintain the peripheral blood count at a reasonable level. Therefore, in patients who need repeated transfusions, it is best to give daily transfusions approximately equivalent in amount to the 24-hour loss. In cases of blood loss from an acute hemorrhage, the situation is different. Here one must replace the blood loss as rapidly as possible. It seems to me that the findings which I am presenting in this case corroborate this concept.

Two things of importance were found in the autopsy. There was a hemorrhagic tendency, which is found frequently in patients with acute leukemia. As a matter of fact, most patients with acute leukemia die of hemorrhage. Secondly, there was extensive systemic involvement, a finding which is difficult to reconcile with the short clinical history. It is, therefore, obvious that this patient had this process going on for a much longer time than the history indicates.

The peripheral blood of this patient at the time of admission revealed a total white blood cell count of 19,000. Of the white cells, about 90 per cent were undifferentiated mononuclear cells which were classified as blast cells. There were only 4 per cent granulocytes. Differentiation of the blast cells must be done under high magnification. In this way (Fig. 1) one sees the nucleus to be indented; the structure and shape suggest that we are dealing with monoblasts. The presence of these cells does not by itself justify the diagnosis of monocytic leukemia, because in some cases of acute granulocytic leukemia the predominant cell may be a monoblast or immature monocyte. In this latter condition, there are certain clinical differences. Also, during the patient's hospital admission a sternal marrow aspiration was done. In this material, there were almost no remnants of normal marrow tissue. The predominant cell present, replacing most of the other elements, was an immature or blast form of the monocytic series, identical to that seen in the peripheral blood. (Fig. 2)

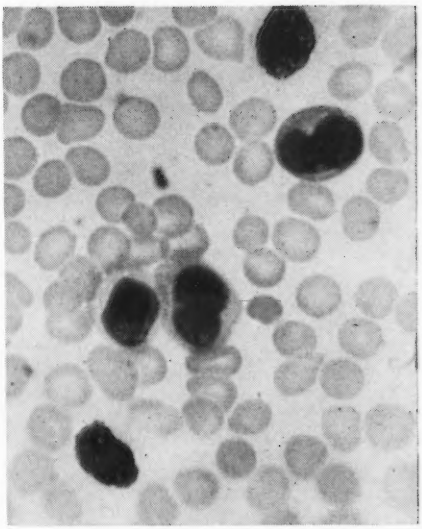

Figure 1.
Peripheral blood smears showing leukemia cells x1100.

In the tissues examined at autopsy, we found extensive infiltration by leukemic cells similar to those seen on the smears. The marrow tissue was almost completely replaced by leukemic cells, and one could identify only occasional nucleated red cells or megakaryocytes.

It is interesting, while reviewing the changes we found throughout the body, to recall that the clinical illness extended back only four weeks prior to death. The proliferation of these cells was found in almost all of the tissues in the body. This was so extensive that it suggested that the body acted as a culture medium for these cells to develop.

The lymph nodes were extensively involved and grossly, in addition to the pallid, fleshy, leukemic infiltration, showed scattered hemorrhage. Microscopically, almost nothing remained of the normal lymph node. Instead, there was diffuse proliferation of leukemic cells which had the same characteristics as the cells in the peripheral blood and bone marrow.

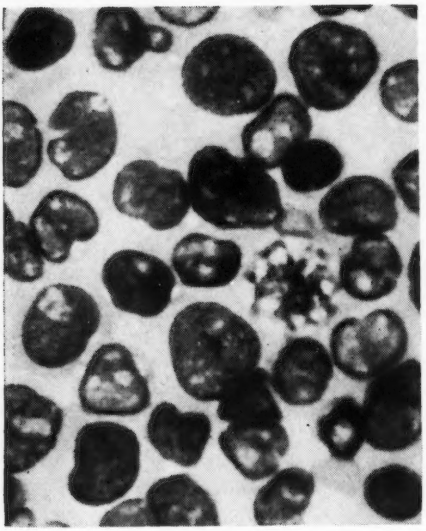

Figure 2.

Sternal marrow aspiration showing predominantly monocytic leukemia cells with kidney-shaped nuclei x1000.

The sinusoids were either engorged by the leukemic cells or destroyed by their infiltration.

The liver was interesting because a characteristic feature was found there. Grossly, we were able to see small areas of leukemic infiltration which were grayish-yellow. Microscopically, there were two interesting findings. (Fig. 3) First, the infiltrating cells were found not only in the periportal zones but also extending diffusely into the sinusoids. In lymphocytic leukemia, there is well defined portal infiltration and in granulocytic leukemia, the infiltration is primarily in the acini. The second interesting feature was what seemed to be a transition of reticulo-endothelial cells or Kupffer cells into leukemic cells. This could be a true histiomonocytic type of leukemia, with the leukemic cells originating from histiocytes or, in the case of the liver, from Kupffer cells. This could also be seen in the lymph nodes and spleen, but not quite so prominently.

The spleen was enlarged. There was marked destruction by leukemic infiltration and proliferation — almost completely destroying the normal architecture. The leukemic cells infiltrated the trabeculae and capsule, giving them a moth-eaten appearance. There was another important finding in the spleen. The leukemic cells infiltrated into the vein walls in the trabeculae, under the lining endothelium, and even into the lumen of the vein. (Fig. 4) This may be interpreted as anatomic evidence of breakdown of the tissue-blood barrier. I shall return to that later.

There was, in all other organs except the brain, a similar diffuse infiltration with leukemic cells. There were also scattered hemorrhages throughout the body. The extensive infiltration in the lungs does not necessarily represent an invasion from the blood stream but is, at least in part, due to transformation of the adventitial cells of the blood vessels or of reticulo-endothelial cells of the lung itself. (Fig. 5) In the midportion of the esophagus, we found a small nodule, which was a myoma arising from the muscle of the esophageal wall. Interestingly, we found that there was leukemic infiltration even in this tumor nodule.

These findings indicate that a tremendous change had taken place in this pa-

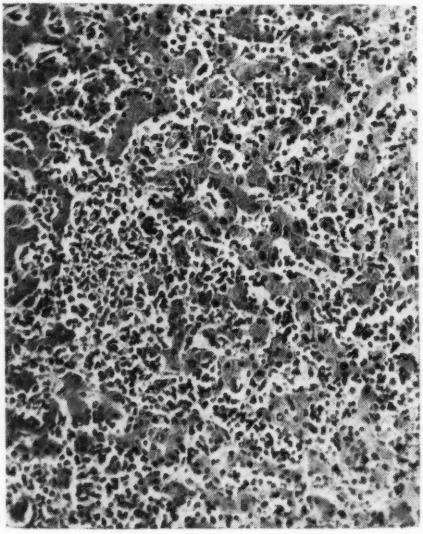

Figure 3.

Liver showing diffuse infiltration with leukemia cells, proliferation of Kupffer cells and degeneration of liver cells x170.

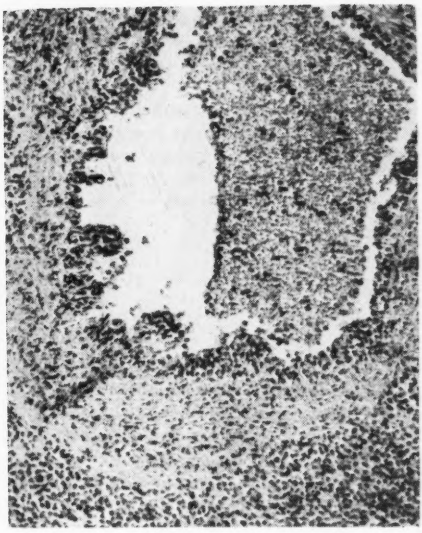

Figure 4.
Vein in spleen showing infiltration of wall and subintimal collections of leukemia cells x150.

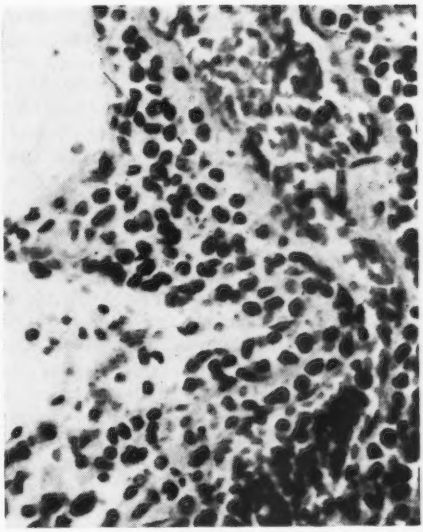

Figure 5.
Lung showing small vessel surrounded by infiltrating and proliferating leukemia cells x550.

tient's body, much of which occurred prior to the time that the clinical manifestations appeared.

There has been much discussion in the literature as to the classification of monocytic leukemia. There are two forms of it. One known as the Naegeli type and the other as the Schilling type. The Naegeli type is thought by some to be a myeloblastic leukemia with a transient period during which monocytes are present in the peripheral blood. The Schilling type is recognized as the true monocytic leukemia. According to another view, both are considered monocytic leukemias; but in the Naegeli type the monocytic cells develop from myeloblast precursors. This is known as the myelo-monocytic leukemia. In the Schilling type, the monocytes develop from reticulo-endothelial cells—a histio-monocytic leukemia. The pathologist can frequently differentiate the two types on the basis of the type of proliferation he observes, namely, either proliferation of reticulo-endothelial cells to monocytes in one case or proliferation of myeloid cells to monocytes in the other case.

It has been stated that granulocytic leukemia comprises about 60 per cent of all leukemias, lymphocytic 35 per cent, and monocytic about 5.6 per cent. Nathan Rosenthal called attention to the similar distribution of the normal white blood cells in the differential count. In a report from the Simpson Memorial Institute of the University of Michigan during the 14 years between 1927 and 1941, including 495 cases, 26.5 per cent were chronic granulocytic and 16 per cent the so-called lymphosarcoma cell leukemia. The latter figure may appear a little high, but it may well be correct. I think that some cases which used to be called chronic lymphocytic leukemia were actually lymphosarcoma cell leukemia. It is easy to overlook a case of lymphosarcoma cell leukemia. They also found the incidence of chronic lymphocytic leukemia to be 15.8 per cent; acute lymphocytic leukemia 11.7 per cent; acute granulocytic leukemia, which actually means acute myeloblastic leukemia, 8.9 per cent; acute myelo-monocytic leukemia 8.5 per cent; acute histio-monocytic, Schilling type, 4.8 per cent; chronic myelo-monocytic, Naegeli type, 4.4 per cent; and chronic histio-monocytic, Schilling type, 3.2 per cent. According to my evaluation, this case belongs to the histio-mono-

cytic, acute, Schilling type, which is found in approximately 5 per cent.

Returning to the interpretation of our findings in this case, it is interesting to consider what happens in a patient like this, in whom a process which has apparently been going on for some time suddenly causes the manifestations of acute leukemia. Is it possible that manifestations began when the blood was first invaded or when more vital organs were first involved? One finding which I find interesting and always try to correlate with the presence of abnormal cells in the blood is the change in the blood vessels, particularly in the spleen. This is not specifically found in leukemia, for it may also be found in infectious mononucleosis and a few of the infectious diseases. I am referring to infiltration by leukemic cells of the walls of the splenic veins and particularly to collections under the intima. In this way, abnormal cells may enter the circulation or pass the tissue-blood barrier. Similar changes occur in lymphosarcoma cell leukemia.

We are dealing here with a rather rare case of monocytic leukemia, which no doubt existed in this patient for a much longer time than the clinical history indicates, and which invaded all tissues of the body except the brain. We found some softening in the brain, which at first made us suspect that it was also infiltrated, but it was only an encephalomalacia and not true invasion of the brain. The so-called barrier between the blood and the brain is so potent that only rarely do we find invasion of the brain by a leukemic process. The invasion of the myoma of the esophagus by the leukemic process is interesting.

Finally, I hope that I was able to convince you that in those cases where one gives repeated transfusions over long periods of time it is not necessary to continue to give these patients an arbitrary amount of a pint of blood, but it is much better to give small amounts very frequently — after one has established a satisfactory blood level.

Cause of Death: Leukemia, acute, histiomonocytic (Schilling type).

Anatomic Diagnoses:

Leukemia, acute, histio-monocytic (Schilling type), involving marrow, lymph nodes, thymus, lungs, heart, esophagus, stomach, ileum, colon, pancreas, kidney, liver, spleen, bladder, prostate, testicles, adrenals, thyroid, and pituitary. **Hemorrhage,** petechial, generalized. **Lungs:** Infarct, recent, right lower lobe; abscess, left lower lobe; bronchopneumonia, organizing. **Bronchi:** Bronchitis, acute. **Esophagus:** Myoma.

Physician: Why was ACTH not given this patient?

Dr. I. Davidsohn: I am afraid that in such a case ACTH is contraindicated. You know that ACTH deprives the patient of some of his defenses. These patients die of one of two things as a rule, *viz.*, hemorrhage and infection. You know what happens to patients who are susceptible to infection, as these patients are, if you give them ACTH. I have never been convinced that ACTH is more than a dubious way of therapy in this type of condition. Of course, giving some of the other agents can prolong life, but very seldom in this type of leukemia does one accomplish more with any of these agents at the present time than one accomplishes with blood transfusions.

Dr. M. M. Kirshen: What type of chemical therapy would you suggest in a condition of the type as presented here today?

Dr. I. Davidsohn: Dr. Sidney Farber has given folic acid antagonists, apparently with good results. Some claim that in this condition one could give urethane. Sometimes one may observe a *miraculous* remission after ACTH treatment.

Dr. D. Atlas: What benefit does the use of protamine sulfate and toluidine blue offer in bleeding patients like this?

Dr. I. Davidsohn: The opinions are divided. We have had much experience with this form of therapy. This patient apparently did not die as the result of the bleeding, even clinically. The hemorrhagic tendency was not extremely pronounced. Please note that when this patient first entered the hospital, the blood study showed a bleeding time of three minutes. That is most unusual for a patient with 90,000 platelets who shows petechiae. That was repeated very carefully and was found to be correct. Another one was done on March 27 and

again the bleeding time was three minutes. I would not believe it if it had not been particularly investigated. There is not always a direct relation between the platelet count and capillary bleeding. In this case, besides the petechial hemorrhages, there was no massive hemorrhage as is frequently seen and which endangers the life of the patient.

Dr. L. Edidin: You found so much diffuse kidney involvment, and yet the urea nitrogen was only 17 mg. per cent.

Dr. I. Davidsohn: When I show a slide to demonstrate leukemic infiltration I will usually choose one that shows marked infiltration. There was enough kidney tissue left to take care of this patient's function.

Dr. E. B. Freilich: I saw a case 10 days ago, on a Sunday evening. I was called to see a woman, 32 years old, who six days prior to the time I saw her, had received a wound from a rusty nail in her thumb. She received penicillin but not anti-tetanus serum. That day, she went into convulsions, ran a fever, and was apparently thoroughly conscious until 2:00 P.M. that afternoon when the doctor took her to the hospital. I saw the woman about 8:00 P.M., six hours later. She was in a deep coma and died while I was examining her. The interesting thing about it was this: she was bleeding from the nose and throat and had purpuric spots on the trunk and extremities. The wound on the thumb was glistening and purulent with an area of purpura around it. She had been fairly well until that day, except for the wound. The white count was 65,000. She had an enlarged liver and the only history we got was that she had an anemia. She had a child two years old. My initial diagnosis was overwhelming septicemia from the thumb with a hemorrhagic encephalitis. She had bilateral Babinski signs, bilateral ankle clonus, and convulsions, so I thought of a hemorrhagic encephalitis or meningitis, probably due to the overwhelming septicemia. At autopsy, this woman had an acute leukemia. She had hemorrhages everywhere; the brain showed a diffuse hemorrhagic encephalitis and meningitis.

REFERENCE

Sturgis, C. C. Hematology, Charles C. Thomas, 1948, p. 577.

Experimental Hypertensions —

(Continued from page 67)

mortem examination. Another similarity between spontaneous hypertension in the dog and essential hypertension in man is the recent report that these animals show an increase in plasma VEM and VDM. Preliminary experiments by our research group on the treatment of spontaneous hypertension in the dog with semipurified hog renin suggest that this hypertension responds similarly to experimental renal hypertension. Certainly, spontaneous hypertension in the dog deserves much more study than has been given it to date, particularly since it may represent the same condition in the dog as essential hypertension in the human.

Summary

Certain experimental hypertensions, particularly experimental renal hypertension which may possess at least a partial pathogenesis in common with human essential hypertension, have been produced in animals. Also important has been the finding of spontaneous hypertension, closely resembling essential hypertension, in a small percentage of dogs. Parallel studies in the laboratory and in the clinic which are also advancing our knowledge of cardiovascular renal physiology now show sufficient promise to suggest the possibility that more successful therapies for human essential and malignant hypertensions may be achieved—even within the present decade.

BOOK REVIEWS

RHEUMATIC DISEASES prepared by the Committee on Publications of the American Rheumatism Association: Charles H. Slocumb, M.D., Chairman. Cloth. 449 pages with 126 figures and 63 tables. Philadelphia: W. B. Saunders Company, 1952. $12.00.

This unusual volume has been prepared from material presented at the Seventh Annual Congress on Rheumatic Diseases and includes related material ranging from biochemistry and other basic sciences to clinical pictures, therapy, and rehabilitation. There are twenty chapters—each subdivided several times with material from different authors, all outstanding men in their fields. Many of the current concepts and fields of study are presented and thus this book is of value to the general physician, the student, and research workers in the field. There are no less than 195 contributors to this work and even a cursory glance at the titles of the chapters enables one to realize the great scope of the book. Rheumatic fever and rheumatoid arthritis are covered completely from the clinical, endocrinologic, orthopedic, therapeutic, and differential diagnostic approaches. The last five chapters are devoted solely to laboratory and other investigative material. Some of the articles are followed by discussions, others by abstracts of related articles, and in general, most of the material is well written and edited. This book offers a novel and refreshing approach to the study of rheumatic diseases and is recommended both as a current reference and as a worthwhile review of current thoughts in the field.

* * * *

PHARMACOLOGY IN CLINICAL PRACTICE by Harry Beckman, M.D. Cloth. First Edition. 839 pages, 152 figures and 49 tables. Philadelphia: W. B. Saunders Company, 1952. $12.50.

Here is a text with an interesting approach to the field of pharmacology, perhaps best described in the author's own words: "I think in terms of specific diseases and the opportunities they present to the pharmacologist, in terms of symptoms and not of anatomical groups of organs or chemical grouping of drugs." Thus, this text approaches the subject from the extremely practical and useful aspect of the disease entity, *i.e.*, according to diagnosis—thereby becoming a handbook of therapy as well as a thorough text of pharmacology. The first section of the book merely lists drugs according to their application. In the second section of the book, the author presents a brief but adequate description of the drugs mentioned in the first section. Once the drug is found, the description is quite complete—including clinical effects, fate in the body, administration, side effects, toxicity, *etc.* The book covers all fields of medicine and therefore is suited to the practicing physician as well as the student, who needs a ready reference which will not only describe the proper drug to use, but provide an understanding of the pharmacological mechanisms involved. The author's fine sense of humor adds to the excellence of this book.

THE SCALP IN HEALTH AND DISEASE by Howard T. Behrman, A.B., M.D. Cloth. First Edition. 566 pages with 312 illustrations. St. Louis: The C. V. Mosby Company, 1952. $12.75.

This well written and easily read text is a study of the scalp first in health—including its anatomy, embryology, physiology, and care; and second in disease—including alopecia, the seborrheic diatheses, infections, and new growths. Other interesting chapters discuss scalp involvment secondary to skin or systemic diseases and scalp disorders of psychogenic origin. There are many other notable features, one of which is a valuable formulary at the end of the book. The almost 100 pages devoted to the embryology, anatomy, and physiology are exceptionally interesting and well presented. The discussion of the many disease entities is complete and includes the etiology, pathology, symptoms, findings, and therapy of almost all the diseases described. This book is an up-to-date, interesting, well-written summary of the material and is recommended to dermatologists in particular, as well as to general practitioners and students.

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DISEASES OF THE CHEST by T. Royle Dawber, M.D., and Lloyd E. Hawes, M.D. Cloth. First Edition. 440 pages with 216 illustrations. Baltimore: The Williams & Wilkins Company, 1952. $10.00.

This book combines the knowledge and experience of an internist (Dr. Dawber) and a roentgenologist (Dr. Hawes), with unusually good results. It is the text's aim to fulfill "the general physician's need for a complete, authoritative, yet simple guide to diseases of the chest and the uses of x-ray." The authors have succeeded admirably in reaching their goal. The organization of the book is straightforward and logical, and the text reads very smoothly. An easy correlation of plates with text is provided by having each even numbered page consist of x-ray plates, the films being unusually clear and well reproduced. Both authors write with brevity and clarity and each disease entity is covered thoroughly, including symptoms, signs, roentgenological findings, some pathology, and a complete description of all possible diagnostic aids. The book is recommended not only to the general practitioner, but also to the upper-class student who is seeking a refreshing and complete approach to the complex field of diseases of the chest.

* * * *

TOXEMIAS OF PREGNANCY by William J. Dieckmann, S.B., M.D. Cloth. Second Edition. 710 pages with 85 illustrations and one color plate. St. Louis: The C. V. Mosby Company, 1952. $14.50.

This excellent text needs no introduction to men in the field of obstetrics. The statement that this second edition has thoroughly incorporated the vast amount of work recently done in the study of the toxemias of pregnancy will hardly be a surprise to anyone. Dr. Dieckmann describes the objectives of his text as two-fold:

to acquaint the (1) obstetrician and (2) the investigator untrained in obstetrics with some of the recent contributions in the study of the pathology and physiology of obstetrics. The book fulfills these objectives well. It contains smoothly written summaries of the pertinent experimental studies which relate to the subject at hand. After covering the basic science material with remarkable completeness, the etiology, clinical aspects, treatment, and postnatal aspects of toxemia are covered with the same adroitness. It is obvious that here is a text which is a must for all men practicing or studying obstetrics, and which will serve both as an interesting study and excellent reference for anyone who has need for information in the field of toxemias of pregnancy.

* * * *

ELECTROCARDIOGRAPHY IN PRACTICE by Ashton Graybiel, M.D., Paul D. White, M.D., Louise Wheeler, A.M., and Conger Williams, M.D. Cloth. Third Edition. 378 pages with 294 figures. Philadelphia: W. B. Saunders Company, 1952. $10.00.

This book is well adapted to the field of electrocardiography in that its text is thoroughly supplemented with many excellently reproduced tracings to illustrate the written material. These electrocardiograms include a section in the last part of the book composed of an excellent series of tracings with the pertinent clinical data provided — presented as diagnostic problems to the reader. The first sections of the book are devoted to an interesting and useful description of the principles and methodology of electrocardiography, including a thorough study of the normal tracing. Brief mention is made of vectorcardiography, but since the method is not in common use at present the material is not fully developed. The middle sections are devoted to diseases of the heart under the headings of: "Disorders of Rhythm and Conduction," "Electrocardiographic Alterations Due to Drugs and Chemicals," "Electrocardiographic Patterns," and "Etiologic Types." The text reads well and supplies brief and adequate descriptions of the clinical aspects of the pathologic states described, and is supplemented with many practical cases and tracings. It is recommended to the student and general practitioner for its vast amount of illustrative material and easily read adequate text material.

* * * *

THE PRINCIPLES AND METHODS OF PHYSICAL DIAGNOSIS by Simon S. Leopold, M.D. Cloth. First Edition. 430 pages with 371 illustrations and 19 color plates. Philadelphia: W. B. Saunders Company, 1952. $7.50.

This is one of several new texts in the field of physical diagnosis. Its primary aim is the "Correlation of physical signs with physiologic and pathologic changes in disease." Thus, there is a good deal of text devoted to physiology (concisely and adequately presented) and many excellent illustrations of how gross pathological findings correlate with physical findings. There is an interesting chapter on "Sounds from the Thorax: Acoustic Principles" by Professor S. Reid Warren, Jr. of the Moore School of Electrical Engineering of the University of Pennsylvania. This chapter provides an interesting description of the basic principles of acoustics and is highly enlightening. The book is well illustrated, neatly written, and rather complete, though often brief; but this latter is in keeping with the purpose of providing a text for medical students who are first approaching physical diagnosis. To complete the text there are two short chapters dealing with the psychiatric survey and history taking. In summary, this book provides a well illustrated, general text in the field of physical diagnosis.

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SIGNS AND SYMPTOMS edited by Cyril Mitchell MacBryde, A.B., M.D., F.A.C.P. Cloth. Second Edition. 783 pages with 98 illustrations, 50 charts, and 8 color plates. Philadelphia: J. B. Lippincott Company, 1952. $10.00.

This book boasts 26 outstanding contributors including Dr. Arthur L. Shapiro of The Chicago Medical School's Department of Dermatology. It approaches medicine as the physician approaches the patient and adds much excellent material concerning pathologic physiology. There are 31 chapters with such titles as: "Pain", "Abdominal Pain", "Jaundice", and "Pathologic Bleeding." Each chapter introduces its problem with a background of basic material and then proceeds to discuss the differential diagnosis involved, adding at the end many recent and pertinent references. The material is well written and logically presented and is valuable as a guide toward reasonable considerations in any medical problem, always with an eye on fundamentals. Many of the chapters are particularly noteworthy, including those on jaundice by Dr. Sidney A. Portis, nervousness and fatigue by Dr. Edwin F. Gildea, pathologic bleeding by Dr. Benjamin Alexander, hematemesis and melena by Dr. Leon Schiff, and pain by Dr. MacBryde. The book has been generally improved and brought up to date, and is recommended as a well written treatise with a practical approach to the problems of the physician.

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ELEMENTARY MEDICAL STATISTICS by Donald Mainland, M.B. Paper. First Edition. 327 pages. Philadelphia: W. B. Saunders Company, 1952. $5.00.

Here is a book which attempts to fill a gap in the education of most doctors: statistics. This book is partially aimed at aiding those physicians who desire to do research, but its main objective is to aid the physician and student to evaluate what he reads. For many years, the average physician has been unable to appreciate data set before him, resulting in the perpetuation of many misconceptions and much illogical thought. Mainland's text is ideally suited for those who realize their shortcomings in the field of statistics and are anxious to remedy the defect. The book is concise, logical, clearly written, and easy to read. We urge all our readers to get this book and read it through slowly at least once, for we feel that the book will make far more intelligent, critical, and wiser readers of all of us.

ABSTRACTS SECTION

EDITOR'S NOTE: The purpose of the Abstracts Section is to acquaint our readers with some of the work being done by our faculty and alumni. We publish, here, abstracts of articles written by members of the faculty and alumni of The Chicago Medical School that are published in other medical journals. Authors are urged to submit abstracts of their articles, 150-200 words in length, to the Editor as soon as possible after publication.

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ESSENBERG, J. M., FAGAN, L., and MALERSTEIN, A. J. Chronic Poisoning of the Ovaries and Testes of Albino Rats and Mice by Nicotine and Cigarette Smoke. West. J. of Surg., Ob. and Gyn., 59:27-32, 1951.

The experimental animals consisting of 50 nicotine injected white rats and 36 strain A mice exposed to cigarette smoke, were divided according to length of treatment into three groups: first, of two to three months treatment; second, of six to eight months treatment; and third, those treated for one year and over. The results can be summarized as follows:

The ovaries of mice proved to be the most susceptible to the nicotine treatment. Follicular destruction was found in some of the ovaries of the first group. Drastic reduction in the number of follicles, formation of corpora atretica and inactivation of the germinal epithelium characterized the ovaries of the mice of the second group. The third group was similar to the second one except that the destruction was more advanced.

The testes of the rats were next in susceptibility. Only minor pathology was noted after three months of treatment. Nearly all of this group fertilized normal females at the end of the treatment. Destruction of the seminiferous epithelium and the reduction of the interstitial cells was found in the second and third groups. The mating of those males to normal females gave a fertility rate of less than one-half.

The ovaries of rats proved to be the most resistant to the effects of nicotine. No definite pathology could be registered in the first group. In the second group, follicular reduction, damage to the germinal epithelium, and enlargement of medullary blood vessels were common. In the third group, neither normal appearing follicles nor corpora lutea were found. The medulla was the largest part of the ovary and it was filled with sinusoid-like blood vessels. The mating of the females to normal males of the first group gave some reduction of fertility, but not a significant one; in the second and third groups, from 30 to 70 per cent of the rats remained sterile.

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FISH, HAROLD S., and GILMAN, J. A Study of the Changing Bone Marrow Picture of the Infant White Rat. (Introduced by John J. Sheinin). Anat. Rec., v. 112, no. 2, February. Paper presented at the American Association of Anatomists, Providence, R. I., March 19-21, 1952.

Marrow counts have been made on more than 150 individuals from 25 litters of rats between birth and sixty days of age. We have found that the marrow of one day old animals is predominantly myeloid (2 to 1) as in the newborn human infant. At forty-eight hours, however, myeloid and erythroid cells show a 1 to 1 ratio. By the end of the fourth day, an increasing erythyroid predominance attains a peak of 3.66 to 1 myeloid cell. A steady fall from this ratio follows through the seventh day (2.2 to 1). On the eighth and tenth days, two lesser peaks are reached with an intervening decline. After ten days, an oscillating decline of erythropoietic cells occurs until the myeloid elements again predominate usually between thirty and sixty days after birth.

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FOA, PIERO P., SANTAMARIA, L., BERGER, S., SMITH, J. A., and WEINSTEIN, H. R. Effects of the Hyperglycemic-Glycogenolytic Factor (HGF), Epinephrine and Insulin in Normal and Depancreatized Dogs. Proc. Soc. Exper. Biol. and Med., 80:635-639, 1952.

Experiments were performed to investigate the hypothesis that the Hyperglycemic Factor is a second pancreatic hormone involved in the regulation of the blood sugar. The results of the experiments suggest the following conclusions: 1. The hyperglycemia produced by HGF and by epinephrine in the depancreatized dog with ketosis is greater in animals with mild ketosis than in animals with severe ketosis. 2. Since ketosis is believed to increase as liver glycogen decreases, these results suggest that the hyperglycemic response to HGF and epinephrine depends upon the amount of liver glycogen present. 3. In the well controlled depancreatized dog without ketosis, on the other hand, the hyperglycemic effect of HGF is greater than in the normal animal, suggesting that in the presence of the pancreas, the action of HGF is limited by the secretion of insulin. 4. Similarly, in the well controlled depancreatized dog without ketosis, the hypoglycemic effect of insulin is greater than in the normal animal, suggesting that in the presence of the pancreas the action of insulin is limited by the secretion of HGF. 5. It is suggested that HGF and insulin might be two mutually regulated pancreatic hormones and that their balanced secretion might be an important factor in the maintenance of a normal blood sugar concentration.

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GOLDFARB, A. R. Peptide Structure and Denaturation of Proteins. Science *114*:177 (1951).

On rapid heating of a dilute solution of protein in water a marked rise in optical density occurs followed by a gradual fall. This preliminary data is interpreted in terms of a theory of denaturation.

KOENIG, HAROLD, FELDMAN, D., and KOENIG, R. S. Ultraviolet and phase contrast photomicrography of living cells grown in vitro[1]. Anat. Rec., v. 112, no. 2, February. Paper presented at the American Association of Anatomists, Providence, R. I., March, 1952.

A variety of chick embryo tissues including brain, spinal ganglion, liver, and heart were grown in tissue culture on quartz cover slips employing the Maximow double cover slip technique. Photomicrographs of living cells were obtained with a phase microscope and with an ultraviolet reflecting microscope at wavelengths 2537A, 2800A and 3130A, isolated by means of a grating monochromator. Focusing was accomplished in visible light to minimize exposure of the cells to ultraviolet light. In many instances, preparations were fixed, rephotographed and stained to determine the influence of fixation on cell structure. The ultraviolet microscope provides information on the morphological distribution of nucleic acids and protein in the living cell and shows the alterations produced by fixation which can be compared easily with the stained preparations.

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KOENIG, RUTH S. and KOENIG, H. An experimental study of post mortem alterations in neurons of the central nervous system. J. of Neuropath. and Exp. Neur., 11:69-78, 1952.

Animals were fixed by vascular perfusion at varying intervals post mortem after preliminary washing out of the blood. Perceptible changes in neurons seen at one-half hour post mortem consisted of cell swelling, fragmentation of Nissl bodies, and loss of basophilia. These changes progressed with time. From three hours post mortem on, cytoplasmic vacuoles were seen. At twenty-three and one-half hours post mortem nuclear disintegration was pronounced and cell margins were indistinct. Shrinkage and hyperchromatosis of neurons occurred in small blocks freshly fixed by immersion, and in large blocks near the surface. Nerve cells, some distance from the surface of immersion-fixed tissue blocks, showed autolytic changes in the form of swelling, fragmentation of Nissl substance, loss of basophilia, and occasional vacuoles. Methods of fixation to avoid post mortem and fixation artifacts were discussed.

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KOPPER, PAUL H. The Reduction of Formaldehyde by Bacterial Cells. J. Gen. Physiol. *34* (5): 53 (1951).

Formaldehyde is reduced to methyl alcohol by living cells of a creatinine-decomposing strain of *Pseudomonas aeruginosa*. Recovery is close to 100% when the reaction takes place at 3°C., but fluctuates between 25 and 75% at 37°C. The amount of HCHO taken up in 30 min. by 3×10^{10} cells of the organism was termed its reducing capacity. It was found to be 400 to 480 mg. at 37°C. The reaction takes place over wide pH and temperature ranges and is independent of the concentration of HCHO as long as the latter is not high enough to exert a toxic effect on the cell. A decrease in reducing capacity is noted with organisms harvested in their late stationary phase of growth. In older cultures, the number of viable cells determines the amount of HCHO taken up. N/100 NaOH depresses the reducing capacity of the organism without affecting bacterial viability. Exposure of bacterial suspensions to temperatures of 46-52°C. for 10 min. causes a more rapid decrease in the number of viable cells than in reducing capacity. Incubation of bacterial suspensions with nutrient substances, which are able to support adequately the growth of the organism, for 30 min. prior to the addition of HCHO, induces increases in reducing capacity. The uptake of HCHO by different microorganisms seems to be related to their gaseous and nutritional requirements. For example, strains of *P. aeruginosa* and *P. fluorescens* are predominantly aerobic, able to utilize a large variety of oxidizable carbon compounds for growth, and most active against HCHO, while *Clostridium perfringens*, an obligatory anaerobe, is very fastidious in its nutritional requirements and takes up no HCHO. Acetaldehyde, instead of being reduced to C_2H_5OH, is oxidized to CH_3COOH by the strain of *P. aeruginosa* studied.

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STRONG, LEON H. Early Stages in the Gross Pattern of Vascular Development of the Choroid Plexus of the Fourth Ventricle in the Rabbit. Anat. Rec., v. 112, no. 2, February. Paper presented at the American Association of Anatomists, Providence, R. I., March 19-21, 1952.

A series of cleared embryos and thick sections, injected while living, through the umbilical vein, shows the choroid plexus grossly. In the 11 and 12 day stages, before the basilar artery is in definitive form, several arteries arch around the rhombencephalon from it. Their end arteries vascularize the roof. By the middle of the 13th day the pontine flexure is well developed. One of these arteries lies against the caudally overhanging ependymal roof next to the rhombic lip, in the groove between the pons and medulla. Arrival just lateral to the midline dorsally this artery turns caudally, spreading a plexus as far as the obex, which vascularizes the whole roof. The first definite indication of the choroid plexus occurred in the 14 day three hour embryo, at the caudal turn of the artery from the pontomedullary groove. Five craniocaudally arranged transverse invaginations of the ependymal roof were present, the most cranial extending into the lateral recess. From this stage on through the 19 day embryo when the choroid plexus is extensively developed, the plexus invaginates deeper into the ependyma; laterally, into the lateral recess, into about 13 tufted leaflets, and dorsally into about 7, in series caudally.

Caudal to the median bilateral plexuses the capillaries of the midline area of the roof disappear during the 15th-16th day, leaving a nonvascular area, Magendie's "foramen".

1. Supported by a grant from the U. S. Public Health Service.

SCHOOL NOTES AND NEWS

DR. SNAPPER APPOINTED TO FACULTY

President John J. Sheinin has announced the appointment of Isadore Snapper, M.D., as Professor of Medicine. It is with great pride that the *QUARTERLY* joins the Faculty and student body in wishing a warm welcome to Dr. Snapper.

Born January 5, 1889, Dr. Snapper was educated in The Netherlands and received the degree of Doctor of Medicine from the University of Amsterdam in 1911. He continued his scientific career at Groningen as a Resident and Associate in Medicine from 1913 to 1917. During this time, and for several years thereafter, Dr. Snapper was engaged in research in London and Amsterdam, as well as in Groningen. His appointment as Professor of Medicine and General Pathology at the University of Amsterdam followed in 1919; a position which he held until 1938.

During this period of time, Dr. Snapper's reputation had spread to this country and several invitations were accepted to present lectures at leading medical centers in the United States. In 1938 he received an appointment at Peiping Union Medical College as Professor of Medicine, and continued his work until he was captured by the Japanese. While in military custody for eight months, he continued his preparation of a book on Bone Diseases. This work was published following his release. During the remainder of the war, he served as The Netherlands' delegate to the United Nations Food Conference, as a Consultant to the Office of the Surgeon General in Washington, D.C., and as a medical advisor to the Commissioners of The Netherlands East Indies.

In 1944, Dr. Snapper took up permanent residence in New York as Director of Medical Education at The Mount Sinai Hospital. In addition to this post, he accepted an appointment as Clinical Professor of Medicine at Columbia University College of Medicine. Both of these positions were held until his appointment early this fall as Director of Medical Education of the Cook County Hospital.

To his colleagues in the field of medical science, Dr. Snapper is often considered a "Consultant's Consultant." Dr. Snapper has always sought to share his own clinical acumen with his numerous students, and it appears to us that teaching is one of his favorite occupations. This desire has led him to accept an appointment to the faculty of The Chicago Medical School.

The *QUARTERLY* takes this opportunity to again extend its sincere congratulations to Dr. Snapper on his recent appointment. We trust that his association with The Chicago Medical School will be close and fruitful.

NEW FACILITIES AVAILABLE

The completion of the new Mount Sinai Research Building now affords both the Faculty and student body of The Chicago Medical School numerous benefits. Two floors of this eleven-story structure have been allocated to The Chicago Medical School. On the second floor are located the offices of the departments of Medicine, Surgery, Pediatrics, Obstetrics and Gynecology, and Neurology and Psychiatry, as well as Classrooms to be used for courses given to Junior and Senior students at The Mount Sinai Hospital. In addition, there is a clinical laboratory where Medical and Surgical clerks will be able to perform laboratory studies on their patients. This constitutes a considerable improvement over the former, less adequate facilities that were housed in the hospital building itself. The East Wing of the second floor has been equipped as a Library, providing considerably more space than did the Library in the main hospital building.

Increased facilities for both clinical and experimental research have been provided on the ninth floor, which is shared by the Departments of Cardiology and Oncology. These departments are headed, respectively, by Drs. Aldo A. Luisada and Philippe Shubik. They have also been allocated rooms on the eleventh floor and penthouse for the housing of their experimental animals.

Dr. Luisada has efficiently planned his section so that the East Wing contains experimental research laboratories, including a suite of rooms for animal surgery. Dr. Luisada's vast experience in this field has prompted him to incorporate an animal recovery room for the care of animals post-operatively. In addition, the East Wing houses a specially equipped Electrokymography Laboratory, with equipment built to Dr. Luisada's specifications and financed by a grant from the Chicago Heart Association. The remainder of the Cardiology section provides space for staff laboratories, as well as completely equipped rooms for electrocardiography, phonocardiography, and ballistocardiography.

A prominent feature of Dr. Luisada's new laboratories is the Cardiac Catheterization room. Much of this equipment is newly acquired and is expected to advance even further his studies with catheterization.

Dr. Shubik has also incorporated several interesting innovations in his modernized and efficiently equipped Oncology laboratories. Studies in virology, as it relates to cancer, will be carried on in a newly equipped laboratory. In addition, separate rooms have been planned for the histologic preparation and for the study of tissues. Another improvement is the instrument room, which houses balances, a spectrophotometer, and other related equipment, and is located in an area convenient to the other laboratories of the Oncology deparment.

Isotope and Chemical Laboratories on this floor are being shared by both departments. This will enable both Dr. Shubik and Dr. Luisada to carry on studies initiated in their former, more modestly equipped laboratories.

The addition of these facilities marks another step in the rapid development of The Chicago Medical School and its affiliates as a medical research center.

SIGMA XI

On October 22, 1952, the Society of the Sigma Xi chartered a new Sigma Xi Club at The Chicago Medical School. The installation took place at a dinner meeting held at Kling Hall at which the President, Dr. Piero P. Foa, presided. The other officers of the club are: Dr. Israel Davidsohn, Vice President; Dr. Leon H. Strong, Secretary; Dr. Jay A. Smith, Treasurer; Dr. J. G. Shaffer and Dr. Paul Hurwitz, members of the Executive Committee.

The Society of the Sigma Xi is a national honorary research organization devoted to the advancement of research and science, both pure and applied. The establishment of a Sigma Xi Club here at The Chicago Medical School, is a milestone in the growth of our school as a recognized research center.

The present membership consists of the numerous members of Sigma Xi who are on our faculty plus several members

from the student body.

At the inauguration dinner meeting held in October, there were numerous dignitaries present, including representatives from the Sigma Xi chapters of the University of Illinois, the University of Chicago, Loyola University, and Northwestern University, and the Sigma Xi Club of Abbott Laboratories. The charter was presented to Dr. Foa by Dr. Thomas Park, Professor of Zoology at the University of Chicago.

After the meeting, Dr. Barry J. Anson, Professor of Anatomy at the Northwestern University School of Medicine, presented a talk entitled "The Story of the Great Plague of London." This proved to be a most fascinating and informative lecture.

The Sigma Xi Club of The Chicago Medical School plans to hold frequent research seminars, at which the faculty members will present reports on their current research projects.

FACULTY NEWS

President John J. Sheinin has recently been appointed a member of the Committee on Emergency Medical Service of the Chicago Medical Society.

Department of Anesthesiology

Dr. Bernard K. Galston, Associate in Anesthesiology, is now on leave of absence from the faculty of The Chicago Medical School, having received his commission as Captain in the United States Army Medical Corps. Captain Galston is presently stationed at Fort Sam Houston, San Antonio, Texas.

Department of Medicine

Dr. Sidney Alpert has been appointed Assistant in Medicine.

Dr. Seymour W. Weisberg has been appointed Associate in Medicine.

Drs. Peter Gaberman, Associate Professor of Medicine, Donald H. Atlas, Associate Professor of Medicine, and Harry F. Weisberg, Assistant Professor of Clinical Pathology and Associate in Medicine, have been awarded a grant of $5,508 by the National Heart Institute to be used in the study of "The Mechanism of Congestive Heart Failure."

Department of Obstetrics and Gynecology

Drs. Alfred J. Platt and Howard L. Woolf have been appointed Assistants in Obstetrics and Gynecology.

Department of Pathology

Dr. Israel Davidsohn, Professor and Chairman of the Department of Pathology and Pathologist and Director of Laboratories, Mount Sinai Hospital, has been elected President of the American Association of Blood Banks.

Dr. Harry Weisberg has been elected a member of the Symposium Planning Committee of the American Society of Clinical Pathologists.

Dr. Bernhard Chomet has been appointed Associate in Pathology.

Department of Physiology

Dr. Piero P. Foa, Professor of Physiology, has been awarded a grant of $7,635 by the Office of Naval Research of the Department of the Navy for research in "Some Aspects of Pancreatic Physiology."

Department of Psychiatry

Dr. Maria W. Piers has been appointed Instructor in Psychiatry.

Dr. J. Herbert Maltz has been appointed Assistant in Psychiatry.

Dr. Bernard Rattner has been appointed Associate in Psychiatry.

Department of Radiology

Dr. Martin W. Shaperman has been appointed Instructor in Radiology.

Department of Surgery

Drs. Jordan L. Daniels and Adolph M. Maller have been appointed Instructors in Surgery.

Dr. Philippe Shubik, Assistant Professor and Coordinator of Oncology, has been granted $3,000 by the Illinois Division of the American Cancer Society for secretarial help at the Tumor Clinic of Mount Sinai Hospital. Dr. Shubik has also recently received a grant of $5,000 from the Atomic Energy Commission for the "Study of the Carcinogenic Effect of Beta Radiations." Dr. A. Robert Goldfarb, Associate in the Department of Biochemistry, is collaborating on this project.

Department of Urology

Dr. Herbert S. Doroshow has been appointed Instructor in Urology.

Class of 1940

Congratulations to Dr. Charles J. Morris on his marriage to the former Miss Marjorie Jane Rhine, September 14, 1952.

Class of 1943

Dr. Arnold Berger, of Elmont, Long Island, New York, has just been inducted as a member of the National Gastroenterological Association and was recently appointed Assistant (Visiting) Gastroenterologist at Triboro Hospital. He is also Clinical Assistant Physician and Gastroenterologist at Queens General Hospital, a Fellow of the American Geriatric Society, and a member of the American Academy of General Practice.

Dr. George N. Chucker has accepted a position as a resident in Radiology at the University of Virginia Hospital, Charlottesville, Virginia, commencing January 1, 1953.

Heartiest congratulations to Dr. and Mrs. Philip Kavet on the birth of a daughter, Gael, November 1, 1952.

Class of 1944

Vincent Sarley, M.D., was recently elected as an Associate Fellow of the American College of Chest Physicians.

Dr. Bernard Tumarkin announces the opening of his office for general practice, 120 East 87th Street, New York City.

Class of 1946

Dr. Paul Prager is now serving as a Captain at the U. S. Army Hospital, Camp Atterbury, Indiana.

Dr. Normabelle Helmen Shivley, formerly of South Bend, Indiana, has opened an office at 2326 Cincinnati Street, San Antonio, Texas.

Class of 1947

Congratulations to Dr. and Mrs. Seymour Warman on the birth of a son, Sheldon Todd, on October 21, 1952.

The *QUARTERLY* wishes to acknowledge the receipt of a letter from Dr. Erwin I. Rockowitz. Dr. Rockowitz recently received his commission as a First Lieutenant in the United States Army Medical Corps and is presently stationed in the Panama Canal Zone. Upon completion of a Residency in Otolaryngology at the Harlem Hospital, New York City, Dr. Rockowitz continued his studies in Otolaryngology at the University of Pennsylvania Graduate School of Medicine prior to his entrance into the service.

Class of 1949

Dr. Seymour Werthamer has been awarded a Fellowship by the government of Switzerland, through the Institute of International Education, for research in pathology at the University of Bern.

Class of 1950

Dr. Anthony Fiorica has opened an office for general practice in Coalinga, California.

Congratulations to Dr. and Mrs. Philip Oransky, of Miami, Florida, on the birth of their son, Robert, on May 9, 1952.

Class of 1951

Dr. Marvin S. Freedland announces the opening of an office for the general practice of medicine and surgery at 6271 S.W. 8th Street, Miami, Florida.

Dr. and Mrs. Sanford Gaylord, of Chicago, are to be congratulated on the birth of a daughter, Randy Lynn, October 5, 1952.

Congratulations also to Dr. and Mrs. Melvin M. Pick on the birth of a daughter, Lorraine Inez, on November 28, 1952. Dr. Pick is a resident in Internal Medicine at the Veterans Administration Hospital, Albuquerque, New Mexico.

Dr. Michael L. Horwitz announces the opening of an office for the practice of general medicine at 1 Lincoln Road, Miami Beach, Florida.

Dr. Arthur Lisbin announces the opening of his office at 1815 Morris Avenue, New York City.

Class of 1952

Congratulations to Dr. Sanford I. Cohen and the former Miss Jean Steinbruecker on the occasion of their marriage on November 30, 1952. Dr. Cohen is at present interning at Jackson Memorial Hospital, Miami, Florida.

STUDENT NEWS

Senior Class

The office of President John J. Sheinin has announced that Ernest Aronowitz was the winner of the Senior Scholarship for having attained the highest scholastic average in the Junior year. Congratulations!

The activities of the Senior Class for the coming year have been planned by the Executive Committee with the aid of the entire class. Elected officers include Jesse Greenberg, President; Donald Behr, Vice-President; and Marilyn Schwab, Secretary-Treasurer. Committees already hard at work include the Photography committee, Commencement committee, Social Committee, Jewelry committee, and Dinner-Dance committee.

Congratulations to Julius and Beulah Buchwald on the birth of their second daughter, Lynn Susanne, on December 9, 1952.

Junior Class

It has been announced by the office of President John J. Sheinin that Stanley Bauer was the winner of the Junior Scholarship for having attained the highest scholastic average in the Sophomore year. Congratulations!

Congratulations to Sam and Marilyn Stone on the birth of their first child, Susan Barbara, on July 18, 1952.

Congratulations to Meyer Blatt and the former Miss Rosalind Wallach of the Bronx, New York, on the occasion of their marriage on September 14, 1952.

Congratulations to Edward Etzel of Collingswood, New Jersey, and the former Miss Ruth Eagleson of Pittsburgh, Pennsylvania, who were married on June 21, 1952.

Congratulations to Wallace (Bill) Kalt and the former Miss Lora Leventhal, both of New York City, who were married June 22, 1952.

Congratulations to James McMeel and the former Miss Joan Getzinger, both of South Bend, Indiana, on the occasion of their marriage on June 21, 1952.

Congratulations to Hubert B. Segal of Brooklyn, New York, and the former Miss Yvette Rosenblum of Chicago, who were married on July 18, 1952.

Congratulations also to Jerrold L. Sharroff and the former Miss Helene C. Pincus on the occasion of their marriage on September 14, 1952.

Best wishes to Seymour Fishkin, of Perth Amboy, New Jersey, and Miss Jacqueline Worobow, of Chicago, on their recent engagement. The wedding will be in June.

Best wishes to Arthur Matles of Brooklyn, New York, and Miss Corynn J. Katz of Freehold, New Jersey, on their recent engagement.

Best wishes to Melvin Post of Brooklyn, New York, and Miss Pearl Rae Godow of Chicago. The couple expect to be married this Spring.

Sophomore Class

Congratulations to Miss Alicia Barach, of New York City, on the occasion of her marriage to Mr. Anatole Schwieger, on December 21, 1952.

Congratulations to Melvin Greenblatt, of the Bronx, New York, on his marriage to the former Miss Etya Silverman, also of the Bronx, on September 13, 1952.

Best wishes to Burton Blackman of the Bronx, New York, and the former Miss Elayne Shwide on the occasion of their marriage on December 20, 1952.

Best wishes to Melvin Goldzband, of Chicago, on his engagement to Miss Marilyn Miller, also of Chicago.

Congratulations to Jordan (Joe) Rhodes, of Chicago, on the announcement of his forthcoming marriage to Miss Dena Schwartz, also of Chicago, on March 22, 1953.

Freshman Class

The Freshman Class was brought together for the first time on September 22nd for a week of orientation before starting classes. Orientation Week, an innovation at The Chicago Medical School, was composed of a series of lectures on the problems of medical education, practice, and curriculum. Among the speakers were President John J. Sheinin, Deans Francis J. Mullin and Andrew H. Ryan, other members of The Chicago Medical School faculty, as well as several visitors prominent in the field of medical education. The consensus among the members of the class is that Orientation Week succeeded in its aim

to provide the entering students with an understanding of their responsibilities toward their new field of endeavor.

Under the auspices of the Student Council, temporary class officers were elected on October 4th. Marvin Rosenzweig was elected President; Howard Rose and Sherwin Warren, Vice-Presidents; and Marjorie Barnett, Secretary-Treasurer. Murray Mazur and Mathew Harris were elected Representatives to the Student Council.

Congratulations to Sandy Mossberg and to Miss Phylsie Goldberg, both of Hartford, Connecticut, on the announcement of their engagement. The couple plan to be married early this summer.

ORGANIZATION NEWS

Student Council

Once again, the Student Council is busily at work in its important task of representing the student body of The Chicago Medical School. At the beginning of this quarter, the Student Council held a Freshman orientation meeting, at which the various organizations at the school were introduced to the Freshman Class. At the the same time, the Student Council assisted the Freshmen in selecing their class officers.

At present, the Council is preparing a new Student Directory for publication. The Student Directory, which proved so valuable last year, is being improved by the use of a multigraph machine recently acquired by the school. Mr. Thomas Scanlan's gracious permission and assistance has made it possible for us to use this machine.

In addition to the Directory, the Student Council is again planning for its Annual Spring Dance, which was such a tremendous success last year. It is hoped that this year's dance will far surpass last year's in attendance and congeniality.

The new constitution, which has recently been completed, is awaiting final ratification before it goes into effect. It is hoped that this new constitution will result in a stronger and more efficient Student Council.

The Student Council would like to take this opportunity to express its appreciation to the Student American Medical Association for its generous contribution to the Maurice J. Oppenheim Student Loan Fund.

Stanley Bauer, Secretary

Phi Lambda Kappa

The fall quarter's activities of the Alpha Rho chapter of Phi Lambda Kappa began on the evening of October 4th at the Congress Hotel. The pledge smoker was attended by more fraters, alumni, and prospective pledges than any such meeting in the chapter's history. The gathering was treated to the now famous "White Shoes on Wolcott Street" by fraters Ken Cohen, Hub Segal, and Ted Feldman.

On October 25th, our second annual "Monte Carlo" night was held at the apartment of frater Sheldon Waldman. The social enjoyed its usual success and the event has taken its place as a "must" on the fraternity's social calendar. Our "Women's Auxiliary" sponsored a Halloween Party and Dance, November 1st . . . a real square dance band, colorful decorations, and refreshments, including the traditional cider and doughnuts.

The annual PLK film series, at the "Amph A Theater," was ushered in on October 21st when the first movie entitled "The Embryology of the Eye" was shown. Other films shown included the Armour Film series on Hematology and a new movie on Autonomic Nervous System Drugs. Among the films planned for the coming quarter is one on the "Anatomy of the Arm and Leg." Other prospected films will be listed on the Student Council Bulletin Board.

Arrangements are now being made for Alpha Rho's Annual Maurice J. Oppenheim Memorial Lectureship. Past lecturers have included Irvine Page, Carl Menninger, and Charles K. Friedberg. Another outstanding medical personality has been chosen to address this year's meeting. Look for the announcement in the near future.

Social plans for the future include the annual Induction Dinner to be held at the Sheridan Plaza Hotel, Sunday, January 18th. The following Saturday evening, January 24th, a dance in honor of the Inductees will be held at the Illini Union in conjunction with our brothers of Alpha Alpha chapter of the University of Illinois College of Medicine.

Jerry Gold, Secretary

Phi Delta Epsilon

With the opening of the 1952-53 school session, the activities of the Beta Tau chapter of Phi Delta Epsilon were renewed once more. The chapter is a large and active one, and is planning many events for the near future. To date, several events have taken place. The Phi Delta Epsilon season opened officially with our annual smoker at the Illini Union on October 10th. At that time, many freshmen and upper classmen were entertained by the chapter. Notable among the guests were several faculty members of Phi Dee E, including heads of several clinical departments. This augurs well for the future as it promises an even closer degree of cooperation between the chapter and its faculty advisers, official and unofficial.

The annual pledge dance was given at the Graemere Hotel on November 7th in conjunction with the local chapter of Phi Beta Pi. The chapter is again enrolling a record pledge class of over 25 members, including a number of upper classmen.

Social, educational, and cultural programs are now being formulated for the coming school year. On November 17th, the annual John J. Sheinin Lectureship was given at the Kling Auditorium of Mount Sinai Hospital. The speaker was Charles P. Bailey, noted thoracic surgeon. He discussed the many recent advances in corrective surgery of congenital heart diseases. Dr. Bailey was also feted at a dinner given in his honor by the fraternity.

A series of motion pictures, medical and otherwise, has been planned by the chapter, several of which have already been presented. It is also planned to present a series of lectures on non-medical topics.

Melvin G. Goldzband, Historian

A. I. M. S.

During the early part of the fall quarter, the Chicago Medical School chapter of the A.I.M.S. held meetings at which faculty advisers and national officers had an opportunity to address the membership and student body. In the near future, the chapter hopes to hear from other medical people interested in the A.I.M.S. and its activities.

The main work of the chapter during November and December concerned plans for the national convention held on December 27-29 at the University of Chicago. The convention dealt not only with the educational problems of the medical student, but with his social and economic adjustment as well. At the convention, reports were given by each member chapter — reports covering the local activities and plans. These reports were consolidated into a set of convention "resolutions" which will be distributed to the entire medical student population. These resolutions represent a majority expression of opinion of the convention delegates. There exists no clearer statement of AIMS principles than these yearly convention resolutions.

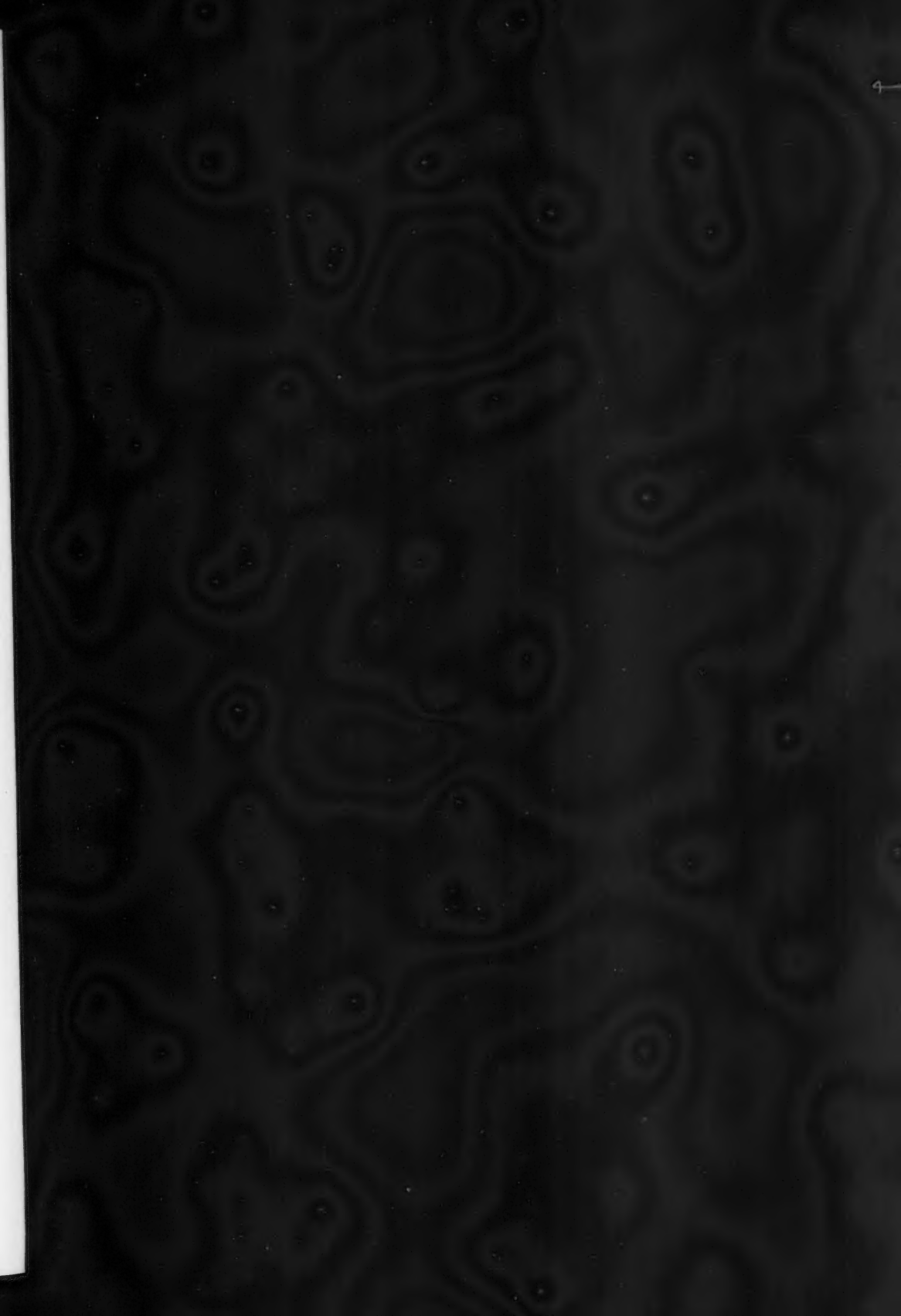
Sanford Lazar, President

Student American Medical Association

SAMA has just completed a new membership drive with the announcement by President Arthur Matles that the number of members has reached an all time high of 200. The educational program of SAMA has consisted thus far of a series of lectures and films presented during the fall quarter. The lecturers included Dr. Louis Schlan, Instructor in Neurology, Dr. Henry H. Fineberg, Associate in Psychiatry, Dr. David B. Radner, Assistant Professor of Medicine (all of The Chicago Medical School), and Dr. Sidney Portis, prominent Chicago gastroenterologist. Plans for the coming quarter call for the continuation of this series of lectures, more details being available on the SAMA Bulletin Board.

In accordance with its desire to take an active role in all projects designed to benefit the student body, SAMA has contributed $25 to the Maurice J. Oppenheim Student Loan Fund which is administered by the Student Council.

Theodore Feldman, Secretary



THE CHICAGO MEDICAL SCHOOL

QUARTERLY

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All articles are accepted on the condition that they are contributed solely to this publication.

A minimum number of illustrations will be furnished by the *QUARTERLY* provided the photographs or drawings are of suitable quality.

Reprints will be furnished by the *QUARTERLY* without charge and must be requested when the manuscript is submitted.

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LECTURE SERIES

The Chicago Medical School — Tuesdays, 12:30 P. M.

710 South Wolcott Avenue — Amphitheater A

SOMATOPSYCHIC RELATIONSHIPS

1953

JANUARY 13 — Somatopsychic Syndromes in General Practice

Dr. Stanley B. Abelson,
Attending Physician, Memorial Hospital, Fairfield, Illinois; Member, Board of Directors, Illinois Academy of General Practice.

JANUARY 20 — Effect of Organic Diseases on the Mind

Dr. Walter C. Alvarez,
Emeritus Consultant in Medicine, Mayo Clinic; Emeritus Professor of Medicine, Mayo Foundation.

JANUARY 27 — Psychological Reactions to Organic Disease

Dr. Ward C. Halstead,
Professor of Experimental Psychology and Director of Medical Psychology, University of Chicago.

FEBRUARY 10 — Mental Reflections from the Skin

Dr. Theodore Cornbleat,
Clinical Professor of Dermatology, University of Illinois; Attending Dermatologist, Cook County Hospital.

FEBRUARY 17 — Facial Deformities and Mental Health: A Socio-Psychological Perspective

Mrs. Frances Cooke Macgregor,
Research Associate in Sociology, Department of Psychiatry; Coordinator, Plastic Surgery Research Project, New York University College of Medicine.

FEBRUARY 24 — Somatopsychic Syndromes Seen by a Neuro-psychiatrist

Dr. Harry H. Garner
Professor and Chairman of the Department of Neuropsychiatry, The Chicago Medical School.